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Synthesis and microbiological activity of some *N*-(2-hydroxy-4-substitutedphenyl)benzamides, phenylacetamides and furamides as the possible metabolites of antimicrobial active benzoxazoles

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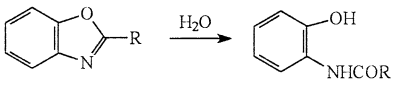
Abstract

The synthesis of some *N*-(2-hydroxy-4-substitutedphenyl)benzamides, phenylacetamides and furamides as the possible metabolites of benzoxazoles (**II$_{1-15}$**) was performed in order to determine their in vitro antimicrobial activity against three Gram-positive bacteria, two Gram-negative bacteria and the fungus *Candida albicans* and their activities were compared with several control drugs. The compounds **II$_{11}$**, **II$_{12}$**, and **II$_{13}$** were found active at a MIC value of 12.5 μg/ml against the Gram-negative microorganism *Pseudomonas aeruginosa*. Most of the compounds show antibacterial activity at MIC a value of 25 μg/ml against the Gram-positive bacteria *Staphylococcus aureus*. For the antifungal activity against *C. albicans*, compound **II$_{10}$** was found more active than the other derivatives. The antimicrobial activity of some of these benzamides, phenylacetamides (**II$_1$** and **II$_{10}$**) which are the possible metabolites of benzoxazoles, was also compared to their corresponding cyclic analogues **III**–**IV**. Compound **II$_{10}$** possesses two dilutions better antifungal activity than its cyclic analogue, benzoxazole **IV**, against *C. albicans*. © 2002 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

Keywords: Benzamides; Phenylacetamides; Furamides; Benzoxazoles; Antimicrobial activity

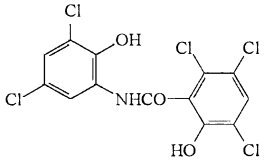
1. Introduction

Benzoxazole derivatives constitute an important class of heterocyclic compounds for their antibacterial and antifungal activities [1–9]. Benzamide derivatives which are the possible metabolites of benzoxazoles show various type of biological properties such as antihelminthic, antihistaminic, antifungal and antibacterial [10–15]. Oxyclozanide, which has a benzamide structure, was discovered in 1969 as an antihelminthic agent effective against *Fasciola hepatica* for the treatment of liver fluke infection [10].



R= H, CH_3

Scheme 1.



Oxyclozanide

We recently reported the antimicrobial activity of some novel *N*-(*o*-hydroxyphenyl)benzamides and phenylacetamides as the possible metabolites of benzoxazoles [15]. Phase I metabolism pathways of benzoxazole in the rabbit involved cleavage of the oxazole ring at the (C–O) linkage on the fused heterocyclic system

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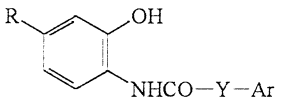


R=CH_3, NO_2 Y= --, CH_2 Ar= Substitutedphenyl, furyl

Fig. 1. ($\mathbf{II_1}$–$\mathbf{II_{15}}$).

by mild hydrolysis and produced *o*-formamidophenol and *o*-acetamidophenol, respectively [16], as shown in Scheme 1, omitting the intermediate stages. According to our previous study, synthesized compounds showed significant antimicrobial effects at MIC values between 12.5 and 50 μg/ml.

In this study, we reported the synthesis and the antimicrobiological activity of several new *N*-(2-hydroxy-4-substitutedphenyl)benzamides, phenylacetamides and furamides ($\mathbf{II_{1-15}}$) (Fig. 1) and their activity was compared to cyclic analogues (**III**–**IV**) (Table 3), assuming that the acetamides would be the possible metabolites of these heterocyclic compounds.

The synthesis of compounds $\mathbf{II_{1-15}}$ (Table 1) was performed by reacting suitable 2-aminophenols with appropriate carboxylic acid chlorides, obtained by treating carboxylic acids with thionyl chloride [5].

The compounds $\mathbf{II_{1-15}}$ were prepared as new products. The structures of $\mathbf{II_{1-15}}$ were supported by spectral data. The IR and ^{1}H NMR spectra are in agreement with the proposed structures. Physical and spectral data of the compounds are reported in Table 1.

2. Experimental procedures

2.1. 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 $\mathbf{II_{1-15}}$. 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.

2.1.1. General procedure for the synthesis of *N*-(2-hydroxy-4-substitutedphenyl)aryl amides

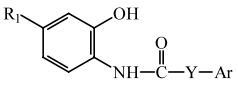
Thionyl chloride (1.5 ml) and appropriate carboxylic acid (0.5 mmol) were refluxed in benzene (5 ml) at 80 °C for 3 h, and then excess thionyl chloride was removed in vacuo. The residue was dissolved in ether (10 ml) and the solution added during 1 h to a stirred, ice-cold mixture of *o*-aminophenol (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. After the precipitate was washed with water, 2 N HCl and water, respectively, and finally with ether $\mathbf{II_{1-15}}$ were obtained. Ethanol–water mixture was used for recrystallization procedure and crystals are dried in vacuo. The chemical, physical and spectral data of the compounds $\mathbf{II_{1-15}}$ are reported in Table 1.

2.1.2. Microbiology

The compounds were dissolved in absolute ethanol (0.8 mg/ml) for both the antibacterial and antimycotic assays. Further dilutions of the compounds and standard drugs in the test medium were prepared at the required concentrations of 400, 200, 100, 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78 μg/ml with Mueller–Hinton broth and Sabouraud dextrose broth. The minimum inhibitory concentrations (MIC) were determined using the method of two-fold serial dilution technique [17,18]. 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 in order to ensure that the solvent per se had no effect on bacterial growth. All the compounds were tested for their in vitro growth inhibitory activity against different bacteria and the yeast *Candida 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 *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.

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

Table 1
Physical properties, preparation and spectral data of the compounds (**II_1–II_{15}**)



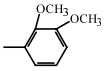
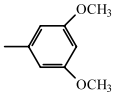
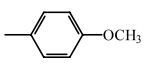
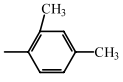
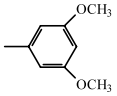
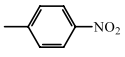
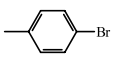
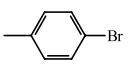
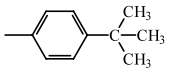
Com. No.	R_1	Y	Ar	Empirical Formula	MP. (°C)	Yield %	IR (cm^{-1})	^1H NMR δppm j=Hz
II_1	CH_3	-		$C_{15}H_{15}O_3N$	196	38	3300, 3295, 2830-2900, 1640, 1111, 950-674	9.98(s, 1H), 9.29(s, 1H), 8.21-8.19(dd, j=1.84, j'=7.87, 1H), 7.46-7.42(m, 1H), 7.07-7.03(dd, j=1.2, j'=7.94, 1H), 6.97-6.95(d, j=8.4, 1H), 6.79-6.77(d, j=8.0, 2H), 6.60-6.58(dd, j=1.94, j'=7.99, 1H), 3.98(s, 3H), 2.21(s, 3H)
II_2	CH_3	-		$C_{16}H_{17}O_4N$	161	45	3305, 3194, 2840-2900, 1645, 1113, 986-744	10.21(s, 1H), 9.25(s, 1H), 7.72-7.69(dd, j=2.0, j'=8.1, 1H), 7.16-7.02(m, 2H), 6.80-6.78(d, j=7.63, 2H), 6.51-6.59(d, j=8.01, 1H), 3.93(s, 3H), 3.84(s, 3H), 2.21(s, 3H)
II_3	CH_3	-		$C_{16}H_{17}O_2N$	162	36	3392, 3140, 2830-2950, 1650, 1118, 859-676	8.67(s, 1H), 7.37(s, 1H), 7.24-7.06(m, 3H), 6.83-6.79(d, j=8.02, 2H), 6.61-6.59(dd, j=8.22, j'=1.98, 1H), 2.38(s, 3H), 2.26(s, 3H), 2.21(s, 3H)
II_4	CH_3	-		$C_{16}H_{17}O_4N$	160	52	3395, 3269, 2820-2910, 1649, 1153, 924-754	8.47(s, 1H), 7.87(s, 1H), 6.92-6.78(m, 4H), 6.63-6.54(m, 2H), 3.76(s, 6H), 2.21(s, 3H)
II_5	CH_3	-		$C_{15}H_{15}O_3N$	165	56	3410, 3008, 2830-2930, 1643, 1103, 899-754	8.70(s, 1H), 8.00(s, 1H), 7.77-7.74(d, j=6.01, 2H), 6.90-6.86(m, 4H), 6.78-6.77(d, j=1.3, 1H), 3.78(s, 3H), 2.20(s, 3H)
II_6	CH_3	-		$C_{16}H_{17}O_2N$	189	48	3410, 3089, 2845-2920, 1643, 1120, 949-880	8.72(s, 1H), 7.42(s, 1H), 7.35-7.33(d, j=7.75, 1H), 7.01-6.69(d, j=6.21, 2H), 6.81-6.79(d, j=1.42, 1H), 2.41(s, 3H), 2.27(s, 3H), 2.21(s, 3H)
II_7	NO_2	-		$C_{15}H_{14}O_6N_2$	259	43	3397, 3095, 2830-2967, 1650, 1586, 1342, 1066, 942-749	10.35(s, 1H), 8.99(s, 1H), 8.39-8.37(d, j=9.0, 1H), 7.73-7.44(m, 2H), 6.97-6.69(d, j=2.0, 2H), 6.58-6.57(d, j=2.0, 1H), 3.78(6H)
II_8	NO_2	-		$C_{15}H_{14}O_4N_2$	231	60	3396, 3092, 2830-2940, 1659, 1507, 1346, 1090, 931-716	8.53(s, 1H), 7.80(s, 1H), 7.79-7.78(d, j=2.0, 1H), 7.72-7.71(dd, j=2.0, j'=8.0, 1H), 7.45-7.42(d, j=9.0, 1H), 7.27-7.12(m, 3H), 2.40(s, 3H), 2.28(s, 3H)
II_9	CH_3	CH_2		$C_{15}H_{14}O_4N_2$	156	56	3360, 3265, 2845-2920, 1640, 1108, 968-710	8.17-8.14(dd, j=1.86, j'=9.64, 2H), 7.75(s, 1H), 7.45-7.43(d, j=8.05, 1H), 6.71-6.55(m, 2H)
II_{10}	CH_3	CH_2		$C_{15}H_{14}O_2NBr$	162	43	3300, 3073, 2860-2940, 1637, 1118, 972-753	8.26(s, 1H), 7.45-7.43(d, j=8.34, 2H), 7.16-6.71(m, 3H), 6.61-6.40(d, j=8.03, 2H), 3.65(s, 2H), 2.17(s, 3H)
II_{11}	NO_2	CH_2		$C_{14}H_{11}O_4N_2Br$	220	48	3344, 3093, 2830-2910, 1665, 1554, 1340, 1011, 940-743	10.66(s, 1H), 9.02(s, 1H), 8.31-8.29(d, j=8.94, 1H), 7.71-7.66(m, 2H), 7.49-7.47(d, j=8.0,2H), 7.33-7.31(d, j=7.8, 2H), 3.84(s, 2H)

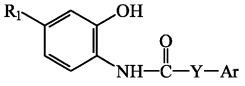
Table 4 (*Continued*)

Com. No.	R_1	Y	Ar	Empirical Formula	MP. (°C)	Yield %	IR (cm^{-1})	^1H NMR δppm j=Hz
II_{12}	CH_3	-		$C_{12}H_{11}O_3N$	167	55	3390, 3048, 2840-2940, 1616, 1109, 952-760	8.67(s, 1H), 8.16(s, 1H), 7.44(s, 1H), 7.17-1.16(dd, j=7.8, j'=2.9, 1H), 6.95-6.93(d, j=8.0, 1H), 6.77(s, 1H), 6.62-6.60(d, j=8.0, 1H), 6.48(s, 1H), 2.20(s, 3H)
II_{13}	CH_3	-		$C_{12}H_{11}O_3N$	158	59	3417, 3044, 2790-2900, 1639, 1115, 943-744	8.44(s, 1H9, 7.98(s, 1H), 7.41-6.77(m, 4H), 6.61-6.59(d, j=8.90, 2H), 2.20(s, 3H)
II_{14}	CH_3	-		$C_{18}H_{21}O_2N$	183	61	3408, 3040, 2830-2960, 1638, 1114, 949-725	8.70(s, 1H), 7.80(s, 1H), 7.74-7.72(dd, j=7.02, j'=2.06, 2H), 7.44-7.41(dd, j=1.90, j'=7.07, 2H), 6.88-6.60(m, 3H), 2.21(s, 3H), 1.27(s, 9H)
II_{15}	NO_2	-		$C_{14}H_{12}O_5N_2$	256	43	3300, 3128, 2860-2940, 1649, 1511, 1378, 1077, 947-742	10.82(s, 1H,), 10.14(s, 1H), 8.61-8.59(d, j=9.0, 1H), 8.17-8.14(d, j=7.8, 1H), 7.74-7.73(d, j=2.8, 1H), 7.70-7.67(dd, j=2.0, j'=8.9, 1H), 7.48-7.41(d, j=8.0, 2H), 7.07-7.01(dd; j=3.0, j'=9.0, 1H), 4.01(s, 3H)

2.2. 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. 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. After incubation for 24 h at 37 ± 1 °C for the antibacterial assay and after incubation for 48 h at 25 ± 1 °C for the antifungal assay, the last tube with no growth of microorganism

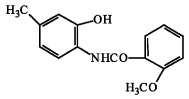
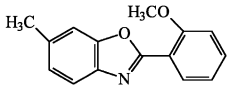
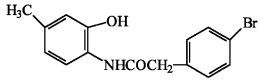
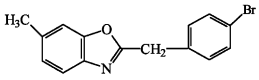
Table 2
The in vitro antimicrobial activity of the compounds (**II_1–II_{15}**) and the standard drugs (MIC in μg/ml)



Comp. number	S.a.	S.f.	B.s.	E.c.	P.a.	C.a.
II_1	100	100	100	50	100	100
II_2	100	100	12.5	100	50	25
II_3	50	50	100	50	50	50
I_4	25	25	50	25	25	25
II_5	25	25	50	100	50	50
II_6	50	50	50	100	100	25
II_7	25	25	50	25	50	50
II_8	50	50	25	25	25	25
II_9	50	50	50	25	200	25
II_{10}	25	25	50	25	50	12.5
II_{11}	25	25	200	50	50	100
II_{12}	25	50	25	50	12.5	25
II_{13}	25	50	50	50	12.5	25
II_{14}	50	50	12.5	25	12.5	25
II_{15}	25	25	100	50	25	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

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

Table 3
Comparison of the antimicrobial activity of the synthesized benzamides, phenylacetamides $\mathbf{II_1}$ and $\mathbf{II_{10}}$ with their cyclic analogues **III–IV** (MIC μg/ml)

Com. No.	Synthesized amides and their cyclic analogues	Microorganisms					
		Gram-positive			Gram-negative		Fungus
		S.a.	S.f.	B.s.	E.c.	P.a.	Ca.
II_1		100	100	100	50	100	100
III		50	50	25	50	50	25
II_{10}		25	25	50	25	50	12.5
IV		50	50	12.5	50	25	50

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.

3. Result and discussion

The antibacterial activity of the compounds and the control drugs shown in Table 2 indicates that the compounds $\mathbf{II_{1-15}}$ inhibit in vitro growth of a number of microorganisms, exhibiting MIC values of between 200 and 12.5 μg/ml. Moreover, Table 2 reveals that most of the synthesized compounds showed antibacterial activity at MIC values of between 25 and 50 μg/ml against the Gram-positive bacteria *S. aureus* and *S. faecalis*. Furthermore, the antibacterial activity of the compounds $\mathbf{II_{1-15}}$ against *E. coli* as Gram-negative bacterium showed lower potencies than the compared control drugs. On the other hand, compounds $\mathbf{II_{12}}$–$\mathbf{II_{14}}$ indicated notable activity, with a MIC value of 12.5 μg/ml against the Gram-negative enterobacter *P. aeruginosa*, which is effective in nosocomial infections and often resistant to antibiotic therapy.

The compounds $\mathbf{II_{1-15}}$ were also tested against *C. albicans* for their antimycotic activity and most of the compounds indicated an antimycotic activity performing MIC values between 12.5 and 50 μg/ml. However, antimycotic potencies of the compared control drugs clotrimazole and haloprogin were found more active than the corresponding compounds, showing MIC values of 6.2 and 3.1 μg/ml, respectively.

Finally, we compared the antimicrobial activity of synthesized benzamide and phenylacetamide derivatives $\mathbf{II_1}$ and $\mathbf{II_{10}}$ with their heterocyclic analogues **III–IV** (Table 3), assuming that they are the possible metabolites of benzoxazoles. Table 3 reveals that compound $\mathbf{II_{10}}$ showed two dilutions better antifungal activity against *C. albicans* and one dilution better antibacterial activity against *S. aureus*, *S. faecalis* and *E. coli* than the corresponding heterocyclic analogue **IV**. On the other hand, compound **III** exhibited one and/or two dilutions better potency against the screened microorganisms than the corresponding aryl amide analogue $\mathbf{II_1}$, which is almost inactive.

It can be concluded that the intensity and duration of microbiological activity can be prolonged since both benzoxazoles and corresponding aryl amides which are their possible metabolites possess the same or similar activity.

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