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Synthesis and microbiological activity of some *N*-(*o*-hydroxyphenyl)benzamides and phenylacetamides as the possible metabolites of antimicrobial active benzoxazoles: part II

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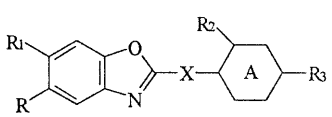
Abstract

The synthesis of some *N*-(*o*-hydroxyphenyl)benzamides and benzacetamides (**2a**–**2p**) in order to determine their in vitro antimicrobial activity against two Gram-positive bacteria, three Gram-negative bacteria and the fungus *Candida albicans* is described. The new compounds were compared with several control drugs. The derivative **2g**, 4-amino-*N*-(*o*-hydroxyphenyl)benzamide, was found active at an MIC value of 25 μg/ml against the Gram-negative microorganism *Klebsiella pneumoniae*. Most of the compounds exhibited antibacterial activity at an MIC value of 25 μg/ml against *Pseudomonas aureginosa*. For the antifungal activity against *C. albicans*, compounds **2e**, **2h** and **2m** were found more active than the other derivatives (MIC 12.5 μg/ml). The antimicrobial activity of some of these benzamide and phenylacetamide derivatives (**2a**, **2b**, **2f**, **2g**, **2h** and **2k**), possible metabolites of benzoxazoles, was also compared with that of the cyclic analogues **3**–**8**. Compound **2f** possesses two dilutions better antifungal activity than its cyclic analogue the benzoxazole derivative **5** against *C. albicans*, while having one dilution better antibacterial activity against *Streptococcus faecalis* and *K. pneumoniae*.

Keywords: *N*-(2,5-Disubstituted)benzamides; Phenylacetamides; Antimicrobial activity; Benzoxazole metabolites

1. Introduction

In the last few years we reported the synthesis and antimicrobial activity of various 2,5-and/or 6-substituted benzoxazoles of general structure shown below, possessing significant in vitro antibacterial activity especially against some enteric Gram-negative rods such as *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and the yeast *Candida albicans* [1–8].



R = H, Cl, NO_2, NH_2, CH_3
R_1 = H, NO_2, CH_3
R_2= H, Cl, F, OCH_3, NO_2, CH_3
R_3 = H, CH_3, C_2H_5, F, Br, Cl, $NHCH_3$, NO_2, NH_2, $C(CH_3)_3$, $NHCOCH_3$, $N(CH_3)_2$, OCH_3
X = —, CH_2, C_2H_4
A = Phenyl, Cyclohexyl, Cyclopenthyl

A review of the literature revealed that Phase I metabolism pathways of benzoxazole and 2-methylbenzoxazole in the rabbit involved cleavage of the oxazole ring at the (C–O) linkage on the fused heterocyclic system by mild hydrolysis and produced *o*-formamidophenol and *o*-acetamidophenol respectively [9], as shown in Scheme 1, omitting the intermediate stages.

Benzamide derivatives show various types of biological properties such as antihelmintic, antihistaminic, antifungal and antibacterial activities [10–13]. Oxyclo-

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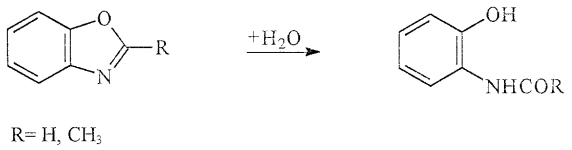
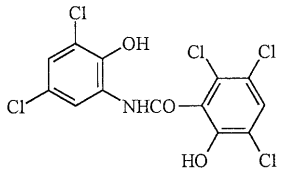


R= H, CH_3

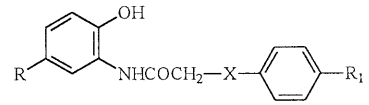
Scheme 1.

zanide, which has a benzamide structure, was discovered in 1969 as an antihelmintic agent effective against *Fasciola hepatica* for the treatment of liver fluke infection [10]. However, there are few published data on the antibacterial and antifungal activity of the benzamide derivatives.



Oxyclozanide

We recently reported some novel active *N*-(2-hydroxyl-5-substituted phenyl)benzacetamide, phenoxyacetamide and thiophenoxyacetamide derivatives with the general structure shown below as the possible metabolites of antimicrobial active benzoxazoles [14]. According to our previous study, synthesized compounds showed significant antimicrobial effects at MIC values between 25 and 100 μg/ml. In general, antimicrobial activity of benzoxazole derivatives has been found to be better than that of their corresponding acetamides, but some acetamide derivatives possessed either the same or improved potency with respect to their cyclic analogues.



X = —, O, S

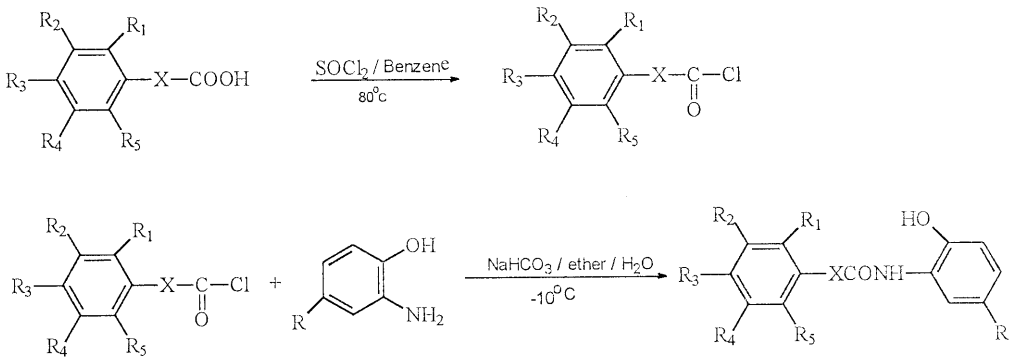
R = -H, -Cl, -CH_3

R_1 = -H, -Cl

In this study, we report the synthesis and antimicrobial activity of several *N*-(*o*-hydroxyphenyl)benzamides and phenylacetamides (**2a**–**2p**) and their activity was compared to that of the cyclic analogues, benzoxazoles (**3**–**8**), assuming that the acetamides would be the possible metabolites of these heterocyclic compounds.

2. Chemistry

The synthesis of the compounds **2a**–**2f**, **2h**–**2k**, **2m**–**2p** was performed by reacting suitable 2-aminophenols with appropriate carboxylic acid chlorides, obtained in turn by treating carboxylic acids with thionyl chloride (Scheme 2). Additionally, the synthesis of the com-



2a-f, 2h-2k, 2m-2p

X= CH_2, —

R = H, Cl, CH_3, NO_2

R_1 = H, CH_3, OCH_3

R_2 = H, OCH_3

R_3 = H, Cl, Br, CH_3, NO_2, OCH_3, $C(CH_3)_3$, F

R_4 = H, OCH_3

R_5 = H, OCH_3

Scheme 2.

pounds **2g** and **2l** was accomplished by reduction of compounds **2d** and **2k** respectively (Scheme 3).

Compounds **2a**–**2p** are new products except **2d**–**2f** and **2p** which have been already described but were obtained by a different synthetic route [15–17]. Melting points of the compounds **2d**, **2e** and **2p** were found to be 204–206°C (lit. m.p.: 224°C), 152–154°C (lit. m.p.: 163°C), [15] and 224–226°C (lit. m.p.: 232–234°C) [16] respectively. Elemental analyses and IR spectral data of **2d** and **2e** were in accordance with the literature [15]. However, the spectral data for the compound **2p** and the physical and spectral data for **2f** synthesized as an intermediate substance were not reported in the literature [17]. Therefore, the physical and spectral data of all the synthesized compounds are given in Table 1; their IR and ^{1}H NMR spectra are in agreement with the proposed structures.

3. Experimental

3.1. Chemistry

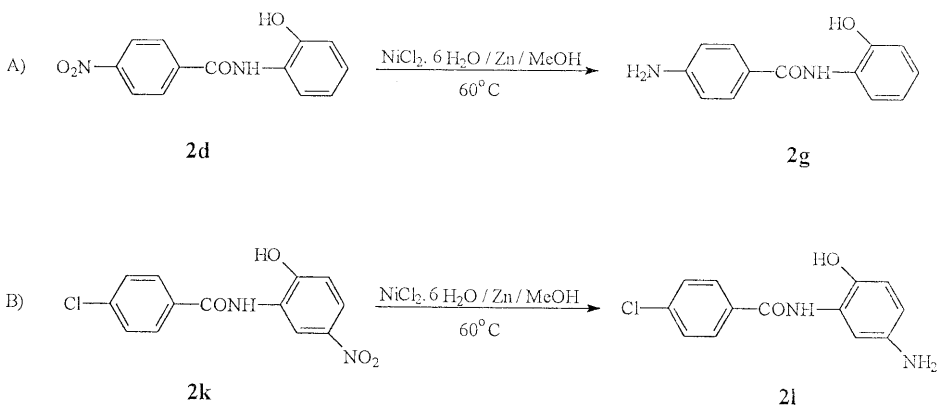
Kieselgel HF_{254} chromatoplates (0.3 mm) were used for TLC and the solvent systems were chloroform:methanol (20:1) for **2a**, **2b**, **2c**, **2d**, **2e**, **2g**, **2m**, **2n**, chloroform:methanol (20:0.4) for **2f**, **2o**, chloroform:*n*-hexane (20:0.3) for **2h**, **2i**, **2j**, **2l**, **2p**, and chloroform:methanol (20:0.6) for **2k**. All the melting points were taken on a Buchi SMP 20 capillary apparatus and are uncorrected. IR spectra were recorded by Perkin Elmer 1330 and Pye Unicam SP-1025 with KBr discs. ^{1}H NMR spectra were obtained with a Bruker NMR type AC-80 MHz spectrometer in d_6-dimethylsulfoxide and TMS was used as an internal standard. Elemental analyses were carried out with a Hewlett Packard 185 CHN analyser. The results of the elemental analyses (C, H, N) were within $\pm 0.4\%$ of the calculated amounts.

3.2. Procedure for N-(o-hydroxyphenyl)benzamides and phenylacetamides (2a–2p)

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 the solution added during 1 h to a stirred, ice-cooled mixture of suitable *o*-aminophenol (0.5 mmol), sodium bicarbonate (0.5 mmol), ether (10 ml) and water (10 ml). The mixture was stirred overnight at room temperature and filtered. The precipitate was washed with water, 2 N HCl, again with water and finally with ether to give **2a**–**2p** except for **2g** and **2l**. The product was recrystallized from methanol for **2a**–**2c**, **2e**–**2f**, **2m**–**2o**, methanol–acetone for **2d**, **2i**, **2j**, **2k**, ethanol for **2h**, and methanol–water for **2p** and dried in vacuo. Compounds **2g** and **2l** were synthesized from **2d** and **2k** respectively, which (5 mmol) were treated with $NiCl_2{\cdot}6H_2O$ (15 mmol) and Zn (40 mmol) in methanol (25 ml) refluxing the mixture at 60°C for 4 h. The precipitate was filtered and the product was recrystallized from methanol.

3.3. Microbiology

For both antibacterial and antimycotic assays, compounds **2a**–**2p** and **3**–**8** were dissolved in absolute ethanol (0.8 mg/ml) [18]. Further dilutions of the compounds and standard drugs in the test medium have concentrations of 400, 200, 100, 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78 μg/ml. The minimum inhibitory concentrations (MIC) were determined using the method of two-fold serial dilution [18,19]. 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.



Scheme 3.

Table 1
Physical properties and spectral data of the compounds

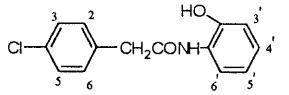
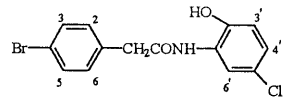
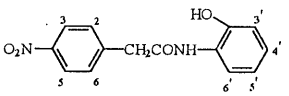
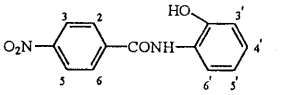
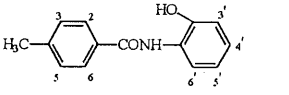
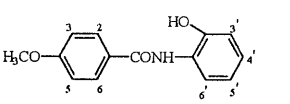
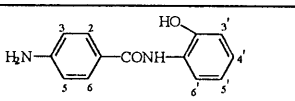
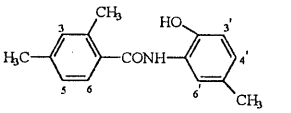
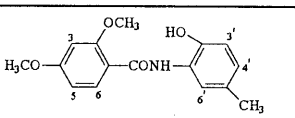
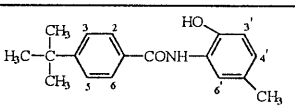
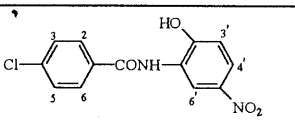
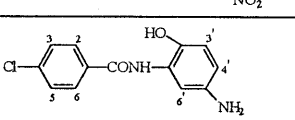
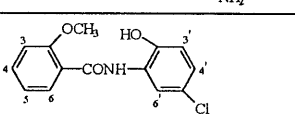
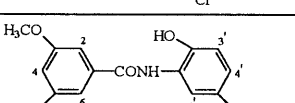
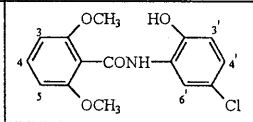
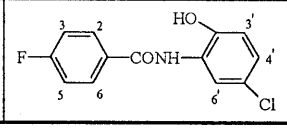
Com. No:	Formula	m.p. (°C)	Yield (%)	IR (cm^{-1})	^{1}HNMR δ ppm
2a		134-137	38.6	3480, 3380, 2870-2930, 1650, 1100	3.74 (s,2H, *CH₂*), 6.40-7.69 (m, 8H, ***aromatic protons***), 9.19 (s,1H, *O-H*), 9.73 (s,1H, *N-H*)
2b		198-200	44.1	3390, 3060, 2850-2930, 1650, 1110	3.72 (s, 2H, *CH₂*), 6.88 (d,2H, *3'-H* and *4'-H*), 7.28 (dd, 2H, *2-H* and *6-H*), 7.50 (dd, 2H, *3-H* and *5-H*), 7.97 (d,1H, *6'-H*), 9.38 (s, 1H, *O-H*)
2c		170-173	40.5	3480, 3320, 2850-2920, 1640, 1530, 1350	3.95 (s, 2H, *CH₂*), 6.56-7.12 (m, 3H, *3'-H, 4'-H* and *5'-H*), 7.50-7.68 (dd, 2H, *2-H* and *6-H*), 7.88 (d, 1H, *6'-H*), 8.15 (dd, 2H, *3-H* and *5-H*), 9.41 (s,1H, *O-H*), 9.81 (s,1H, *N-H*)
2d		204-206	23.3	In accord with the data given in ref.15	6.84 (m, 3H, *3'-H, 4'-H* and *5'-H*), 7.50 (dd, 1H, *6'-H*), 8.03 (dd, 2H, *2-H* and *6-H*), 8.25 (dd, 2H, *3-H* and *5-H*), 9.61 (s, 1H, *O-H*), 9.69 (s,1H, *N-H*)
2e		152-154	34.4	In accord with the data given in ref.15	2.25 (s, 3H, *CH₃*), 6.81 (m, 3H, *3'-H, 4'-H* and *5'-H*), 7.22 (dd, 2H, *3-H* and *5-H*), 7.50 (dd, 1H, *6'-H*), 7.60 (dd, 2H, *2-H* and *6-H*), 9.31 (s, 1H, *O-H*), 9.65 (s,1H, *N-H*)
2f		168-170	62.0	3260, 3480, 2820-2940, 1630	3.84 (s, 3H, *OCH₃*), 6.63-7.10 (m, 5H, *3-H, 5-H, 3'-H, 4'-H,* and *5'-H*), 7.69 (d, 1H, *6'-H*), 7.97 (dd, 2H, *2-H* and *6-H*), 9.44 (s, 1H, *O-H*), 9.69 (s, 1H, *N-H*)
2g		219-221	24.6	3360, 3460, 3250-3390, 1630	5.54 (s, 2H, *NH₂*), 6.50 (dd, 2H, *3-H* and *5-H*), 6.56-7.34 (m, 3H, *3'-H, 4'-H* and *5'-H*), 7.56 (m, 3H, *2-H, 6-H* and *6'-H*), 9.09 (s, 1H, *O-H*), 9.66 (s, 1H, *N-H*)
2h		203-205	54.1	3440, 3100, 2870-2960, 1650	2.06 (s, 3H, *CH₃*), 2.13 (s,3H, *CH₃*), 2.22 (s, 3H, *CH₃*), 6.47-7.50 (m, 6H, ***aromatic protons***), 9.06 (s, 1H, *O-H*), 9.28 (s, 1H, *N-H*)
2i		156-159	34.5	3340, 3180, 2840-2960, 1630	2.22 (s, 3H, *CH₃*), 3.88-4.03 (s, 6H, *OCH₃*), 6.68-6.75 (m, 4H, *3-H, 5-H, 3'-H* and *4'-H*), 8.03 (d, 1H, *6'-H*), 8.22 (d, 1H, *6-H*), 9.81 (s, 1H, *O-H*), 10.38 (s, 1H, *N-H*)
2j		174-175	35.0	3420, 3080, 2880-2970, 1650	1.34 (s, 9H, *C(CH₃)₃*), 2.25 (s, 3H, *CH₃*), 6.81-7.91 (m, 7H, ***aromatic protons***), 9.42 (s, 1H, *O-H*), 9.44 (s, 1H, *N-H*)
2k		248-251	34.0	3380, 3120, 1640, 1530, 1340, 1090,	6.84 (d, 1H, *3'-H*), 7.59 (dd, 2H, *3-H* and *5-H*), 7.94 (m, 3H, *2-H, 6-H* and *4'-H*), 8.84 (d, 1H, *6'-H*), 9.69 (s, 1H,*O-H*)
2l		> 260	31.3	3380, 3480, 3290-3190, 1640	4.69 (s, 2H, *NH₂*), 6.31 (dd, 1H, *3'-H*), 6.66 (d, 1H, *4'-H*), 7.03 (d, 1H, *6'-H*), 7.59 (dd,2H, *3-H* and *5-H*), 7.97 (dd, 2H, *2-H* and *6-H*), 8.43 (s, 1H, *O-H*), 9.53 (s, 1H, *N-H*)
2m		236	30.3	3300, 3140, 2860-2980, 1640, 1095	4.06 (s, 3H, *CH₃*), 6.88-8.56 (m, 7H, ***aromatic protons***), 10.55 (s, 1H, *O-H*), 10.91 (s, 1H, *N-H*)
2n		204-206	54.6	3460, 3240, 2870-2980, 1660, 1100	3.84 (s, 6H, *CH₃*), 6.66-7.22 (m, 5H, *3'-H, 4'-H, 2-H, 4-H* and *6-H*), 7.76 (d, 1H, *6'-H*), 9.47 (s, 1H, *O-H*), 10.03 (s, 1H, *N-H*)

Table 1 (*Continued*)

Com. No:	Formula	m.p. (°C)	Yield (%)	IR (cm^{-1})	^{1}HNMR δ ppm
2o		228-230	39.1	3420, 3040, 2860-2930, 1650, 1110	3.81 (s, 6H, ***CH₃***), 6.62-8.19 (m, 6H, ***aromatic protons***), 9.15 (s, 1H, ***O-H***), 10.13 (s, 1H, ***N-H***)
2p		224-226	57.0	3420, 3080, 1650, 1090	6.81-8.22 (m, 6H, ***aromatic protons***), 9.552 (s, 1H, ***O-H***)

All the compounds were tested for their in vitro growth inhibitory activity against different bacteria and the fungus *Candida albicans* RSKK 628. The origins of bacterial strains were *Staphylococcus aureus* RSSK 250, *Streptococcus faecalis* RSSK 500 as Gram-positive and *Escherichia coli* RSSK 313, *Klebsiella pneumoniae* RSSK 256, and *Pseudomonas aeruginosa* RSKK 356 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 the Faculty of Pharmacy of Ankara University.

Ampicillin, amoxicillin, erythromycine, chloramphenicol, streptomycin, tetracycline, oxiconazole, and haloprogin were used as control drugs. The data on the antimicrobial activity of the compounds and the control drugs are given in Table 2.

3.3.1. Antibacterial assay

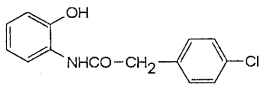
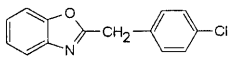
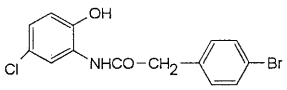
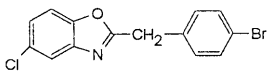
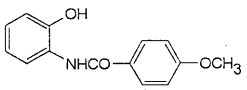
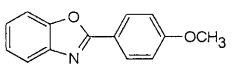
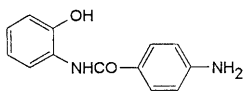
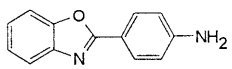
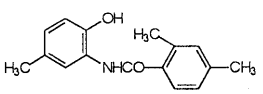
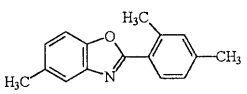
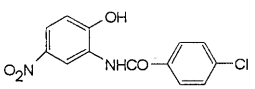
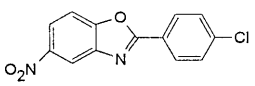
The cultures were obtained in Mueller–Hinton broth (Difco) for all the bacteria after 24 h of incubation at 37 ± 1°C. Testing was carried out in Mueller–Hinton broth at pH 7.4 and the two-fold serial dilution technique was applied. The final inoculum size was 10^5 CFU/ml. A set of tubes containing only inoculated

Table 2
The in vitro antimicrobial activity of the compounds **2a–2p** and standard drugs (MIC in μg/ml)

Comp.	Microorganism [a]					
	Gram-positive		Gram-negative			Fungus
	S.a.	*S.f.*	*E.c.*	*K.p.*	*P.a.*	*C.a.*
2a	50	50	50	50	50	25
2b	50	50	50	50	50	25
2c	50	50	50	50	50	25
2d	50	50	50	50	50	25
2e	25	50	50	50	25	12.5
2f	25	50	50	50	25	25
2g	50	50	50	25	25	25
2h	50	50	50	50	50	12.5
2i	25	50	50	50	25	25
2j	25	50	50	50	25	25
2k	25	50	50	50	25	25
2l	50	50	50	50	25	25
2m	50	50	50	50	25	12.5
2n	50	50	50	50	25	25
2o	50	50	50	50	25	25
2p	50	50	50	50	50	25
Ampicillin	0.39	0.39	1.56	12.5	>400	
Amoxicillin	0.39	0.39	1.56	12.5	>400	
Erythromycine	25	1.56	50	50	25	
Chloramphenicol	12.5	6.25	25	12.5	25	
Streptomycin	3.12	100	1.56	1.56	100	
Tetracycline	0.78	0.78	3.12	3.12	50	
Oxiconazole						6.25
Haloprogin						6.25

[a] Abbreviations: *S.a.*, *S. aureus*; *S.f.*, *S. faecalis*; *E.c.*, *E. coli*; *K.p.*, *K. pneumoniae*; *P.a.*, *P. aeruginosa*; *C.a.*, *C. albicans*.

Table 3
Comparison of the antimicrobial activity of selected amides **2a**, **2b**, **2f**, **2g**, **2h**, **2k** with the cyclic analogues **3-8** (MIC in μg/ml)

Comp. No:	Synthesized amides and their cyclic analogues	Microorganisms[a]					
		Gram-positive		Gram-negative			Fungus
		S.a.	*S.f.*	*E.c.*	*K.p.*	*P.a.*	*C.a.*
2a		50	50	50	50	50	25
3[b]		50	50	50	25	50	25
2b		50	50	50	50	50	25
4[b]		50	50	50	25	25	25
2f		25	50	50	50	25	25
5[c]		12.5	100	50	100	12.5	100
2g		50	50	50	25	25	25
6[c]		12.5	100	25	12.5	12.5	25
2h		50	50	50	50	50	12.5
7[d]		50	50	50	50	50	25
2k		25	25	50	50	50	25
8[c]		12.5	12.5	25	12.5	25	12.5

[a] Abbreviations: *S.a.*: *Staphylococcus aureus*, *S.f.*: *Streptococcus faecalis*, *E.c. Escherichia coli*, *K.p.*: *Klebsiella pneumoniae*, *P.a.*: *Pseudomonas aeruginosa*, *C.a.*: *Candida albicans*.
[b] See reference 2.
[c] See reference 1.
[d] See reference 7.

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.

3.3.2. Antifungal assay

The yeast *Candida albicans* was maintained in Sabouraud dextrose broth (Difco) after incubation for

24 h at 25 ± 1°C. Testing was performed in Sabouraud dextrose broth at pH 7.4 and the two-fold serial dilution technique was applied. The final inoculum 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 yeast was recorded to represent MIC expressed in μg/ml.

4. Results and discussion

The antimicrobial activity of these compounds and the control drugs is shown in Table 2 indicates that the compounds **2a**–**2p** were able to inhibit in vitro growth of a number of microorganisms, exhibiting MIC values between 50 and 12.5 μg/ml.

Table 2 reveals that the synthesized compounds showed antibacterial activity at an MIC value of 50 μg/ml against the Gram-positive bacteria *S. aureus* except the derivatives **2e**, **2f**, **2i**, **2j**, **2k**, which were active at 25 μg/ml. All the synthesized compounds possessed the same potency, 50 μg/ml MIC value, against *S. faecalis*. The activity of the compounds **2a**–**2p** was also tested against *E. coli*, *K. pneumoniae* and *P. aeruginosa* as Gram-negative bacteria. These compounds, against *E. coli* and *K. Pneumoniae*, exhibited lower potency than the control drugs tetracycline and streptomycin, but they showed the same potency as erythromycine. The compound 4-amino-*N*-(2′-hydroxyphenyl)benzamide (**2g**) was the most active against *K. pneumoniae* (MIC value of 25 μg/ml).

As regards antibacterial activity against the enterobacter *P. aeruginosa*, the synthesized compounds **2e**–**2g**, **2i**–**2o** showed significant activity (25 μg/ml MIC value) and possessed better potency than the control drugs streptomycin and tetracycline and showed the same activity as erythromycine and chloramphenicol.

Moreover, the antifungal activity of the synthesized compounds was tested against *C. albicans* and MIC values between 25–12.5 μg/ml were found. Compounds **2e**, **2h**, **2m** were found more active than the other compounds, showing a MIC value of 12.5 μg/ml. However, the control drugs oxiconazole and haloprogin possessed one dilution better potency than these compounds.

Benzamides **2d**–**2p** were found more active than phenylacetamides **2a**–**2c**, in particular against Gram-positive bacteria *S. aureus*, Gram-negative bacteria *P. aeruginosa* and the fungus *C. albicans*. When the MIC values of **2a**–**2c** are compared with the previously synthesized phenylacetamides [14] against *C. albicans*, it is observed that substitution with an atom and/or atom groups at position R_3 possessing electronically positive field effects, such as Cl, Br and NO_2, increases their antifungal activity.

Finally, we compared the antimicrobial activity of synthesized benzamide and phenylacetamide derivatives **2a**, **2b**, **2f**, **2g**, **2h** and **2k** with their heterocyclic analogues **3**–**8** [1,2,7], assuming that they are the possible metabolites of benzoxazoles as given in Table 3.

Table 3 reveals that although most of the benzoxazole derivatives (**3**–**8**) show better antimicrobial activity than the corresponding amides, some amide derivatives possessed either the same or one-fold improved potency. This is the case of compound **2f** which showed one dilution better antibacterial activity than the compared benzoxazole derivative **5** against *S. faecalis* and *K. pneumoniae*. Additionally, compounds **2a** and **2b** showed the same activity as benzoxazole derivatives **3**, **4** against the tested two Gram-positive bacteria and *E. coli*.

As far as activity is concerned, most of the synthesized compounds were as potent as the cyclic analogues **3**–**8**, showing a MIC value of 25 μg/ml against *C. albicans*, except **2f** and **2k**. While compound **2k** showed one-fold less potency than its cyclic analogue, compounds **2f** and **2h** showed better antifungal activity than the compared benzoxazole derivatives.

In conclusion, antimicrobial activity data reported in Table 3 suggest that the pharmacophoric groups in these sets of amides and cyclic analogues could be similar. If these amides are the possible metabolites of the corresponding fused heterocyclics, then we can expect prolonged antimicrobial activity for these derivatives.

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