

Synthesis and Antimicrobial Activity of Some 5-[2-(Morpholin-4-yl)acetamido] and/or 5-[2-(4-Substituted piperazin-1-yl)acetamido]-2-(*p*-substituted phenyl)benzoxazoles

Özlem Temiz-Arpacı^a, Aliye Özdemir^a, İsmail Yalçın^a, İlkey Yıldız^a, Esin Akı-Şener^a, Nurten Altanlar^b

^a Ankara University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Ankara, Turkey

^b Ankara University, Faculty of Pharmacy, Department of Microbiology, Ankara, Turkey

In this study, a series of twelve novel 5-[2-(morpholin-4-yl)acetamido] and/or 5-[2-(4-substituted piperazine-1-yl)acetamido]-2-(*p*-substituted phenyl)benzoxazole derivatives have been synthesized and their structures were confirmed by IR, ¹H NMR, and mass spectral data. These compounds were prepared by reacting 5-(2-chloroacetamido)-2-(4-*p*-substituted-phenyl)benzoxazoles, which were obtained by using 5-amino-2-[*p*-substituted-phenyl]benzoxazoles with chloroacetyl chloride, in the presence of morpholine or 1-substituted piperazines. All synthesized compounds **3–14** were tested by using the method of twofold serial dilution technique for *in vitro* activities against certain strains of Gram-positive, Gram-negative bacteria as well as the yeasts *Candida albicans*, *Candida krusei*, and *Candida glabrata* in comparison with standard drugs. Microbiological results showed that the newly synthesized compounds possessed a broad spectrum of activity, showing MIC values of 3.12–50 µg/mL against the *Candida* species.

Keywords: Benzoxazoles; Antibacterial activity; Antifungal activity; Morpholine acetamide; Piperazine acetamide

Received: July 13, 2004; Accepted: February 6, 2005 [FP923]

Introduction

The rapidly increasing incidence of multiple drug-resistant Gram-positive bacteria requires an urgent discovery of novel active agents against these pathogens [1, 2]. The benzoxazoles have various biological activities such as antibacterial, antifungal [3–12], antimycobacterial [13], antitumoral [14–19], HIV-1 reverse transcriptase [20–26], and topoisomerase I inhibitory activities [27].

A benzoxazole derivative (Figure 1) is significantly more potent as inhibitors of topoisomerase I than camptothecin [28]. UK-1 (Figure 2) is a unique natural bisbenzoxazole product, isolated from a strain of *Streptomyces*, is a magnesium ion-dependent DNA binding agent and inhibitor of human topoisomerase II. It displays a wide spectrum of potent anticancer activities in leukemia, lymphoma, and certain solid tumor-derived cell lines with IC₅₀ values as low as 20 nM [16, 17, 29]. Routiennocin (Figure 3), which is a spiroketal ionophore antibiotic, isolated from a strain of *Streptomyces chartreusis* possessing a benzoxazole ring in its

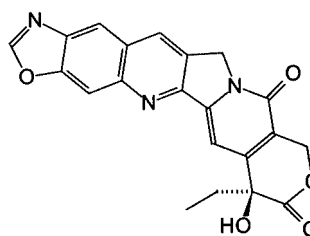


Figure 1. A benzoxazole derivative.

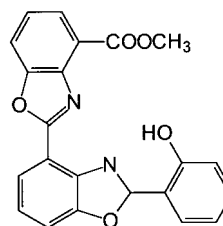


Figure 2. UK-1.

Correspondence: Esin Akı-Şener, Ankara University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, TR-06100 Tandogan, Ankara, Turkey. Phone: + 90 312 223-6940, Fax: + 90 312 223-6940, e-mail: sener@pharmacy.ankara.edu.tr

molecular structure, was found to be very active especially against some Gram-positive bacteria by acting as a good ionophore [4, 30]. Moreover, 5- and/or 6-amidinobenzox-

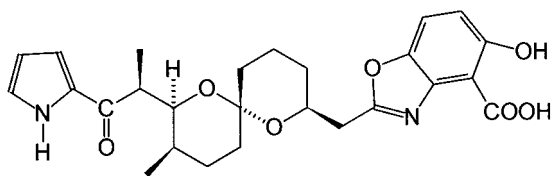
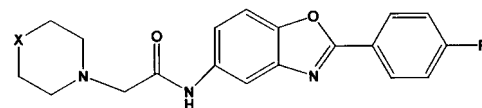


Figure 3. Routiennocin.

azoles as well as benzimidazoles were found as inhibitors of the bacterial KinA/Spo0F. Many of these inhibitors exhibited good *in vitro* antibacterial activity against a variety of susceptible and resistant Gram-positive organisms [25].

In our previous report, we described the preparation and *in vitro* antimicrobial activity of 2-[*p*-substituted phenyl]-5-[2-(substituted phenyl)acetamido]benzoxazole derivatives [31] as seen in Table 1. This time, the substitution, which is attached as acetamido moiety on the C-5 position of benzoxazole ring, has been changed to heterocyclic groups instead of phenyl for the antimicrobial effect. Therefore, a series of novel 5-[2-(morpholin-4-yl)acetamido] and/or 5-[2-(4-substituted piperazin-1-yl)acetamido]-2-[*p*-substituted



X = O, NH, NCH₃

R = H, C₂H₅, F, C(CH₃)₃

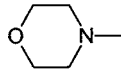
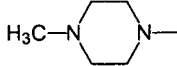

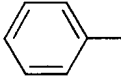
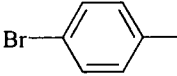
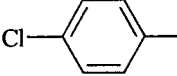
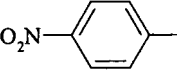
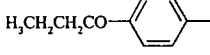
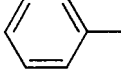
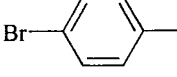
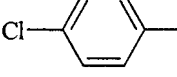
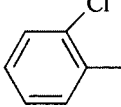
Figure 4. Compounds 3–14.

phenyl]benzoxazole derivatives 3–14 (Figure 4) has been synthesized as the target compounds in order to examine their microbiological activity against various Gram-positive and Gram-negative bacteria and the different yeasts in comparison with several control drugs because in the need of new and different antibacterial agents that are resistant to inactivation by bacterial enzymes. Their structure-activity relationships (SAR) were also studied by using either newly or previously synthesized compounds [31] and the structures of the newly synthesized compounds are supported by spectral data (Table 2).

Table 1. The *in vitro* antimicrobial activity of newly and previously synthesized compounds with the control drugs (MIC in mg/mL).

Comp.	R	A	S. a.	B. s.	E. c.	C. g.	C. a.	C. k.
3	-C ₂ H ₅		50	50	50	25	25	12.5
4	-C ₂ H ₅		50	25	50	12.5	25	12.5
5	-C ₂ H ₅		25	25	50	25	50	6.25
6	-H		25	50	50	25	50	25
7	-H		25	25	50	25	50	25
8	-H		100	100	50	25	50	25
9	-F		25	25	50	25	50	25
10	-F		50	50	50	25	25	50
11	-F		50	50	50	25	25	25

Table 1. (continued)

Comp.	R	A	S. a.	B. s.	E. c.	C. g.	C. a.	C. k.
12	-C(CH ₃) ₃		50	50	50	25	50	6.25
13	-C(CH ₃) ₃		50	50	50	12.5	50	3.12
14	-C(CH ₃) ₃		25	25	50	12.5	25	12.5
15 ^[33]	H		100	50	100	—	50	—
16 ^[33]	H		50	50	50	—	25	—
17 ^[33]	H		100	50	100	—	50	—
18 ^[33]	H		50	200	50	—	25	—
19 ^[33]	H		50	200	25	—	25	—
20 ^[33]	C ₂ H ₅		50	50	50	—	50	—
21 ^[33]	C ₂ H ₅		50	50	50	—	50	—
22 ^[33]	C ₂ H ₅		50	50	50	—	50	—
23 ^[33]	H		50	100	25	—	25	—
Oxiconazole			—	—	—	—	6.25	—
Haloprogin			—	—	—	—	3.125	—
Miconazol			—	—	—	3.125	3.125	1.56
Ciprofloxacin			3.125	1.56	3.125	—	—	—
Gentamicin			3.125	1.56	12.5	—	—	—

S. a.: *Staphylococcus aureus*; B. s.: *Bacillus subtilis*; E. c.: *Escherichia coli*; C. g.: *Candida glabrata*; C. a.: *Candida albicans*; C. k.: *Candida krusei*

Results

A series of twelve 5-[2-(morpholin-4-yl)acetamido] and/or 5-[2-(4-substituted piperazin-1-yl)acetamido]-2-(*p*-substituted phenyl)benzoxazole derivatives has been synthesized by using a two step procedure as seen in Scheme 1. 5-Amino-2-(*p*-substituted phenyl)benzoxazoles (**1**) were obtained by heating *p*-substituted benzoic acids with 2,4-diaminophenol in PPA (polyphosphoric acid) [31]. Amide compounds (**2**) were obtained from 5-amino-2-(*p*-substituted phenyl)benzoxazoles with chloroacetyl chloride [32–34].

5-[2-(Morpholin-4-yl)acetamido] and/or 5-[2-(4-substituted piperazin-1-yl)acetamido]-2-(*p*-substituted phenyl)benzoxazoles (**3–14**) were prepared from amide compounds by reacting with piperazine or morpholine derivatives. All of the derivatives were supported by spectral data. Physical and spectral data of the compounds are reported in Table 2.

To investigate the antimicrobial activity of the synthesized compounds (**3–14**) against two Gram-positive and one Gram-negative bacteria and three *Candida* species were screened using the twofold serial dilution technique. All the

biological results of the compounds are given in Table 1. The combined data reported that the newly synthesized compounds showing MIC values between 3.12–100 µg/mL were able to inhibit the *in vitro* growth of the microorganisms screened.

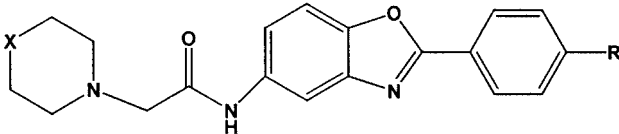
Discussion

Previously, we evaluated the antimicrobial activity of very similar structures which had 2-(*p*-substituted phenyl)-5-[2-(substituted phenyl)acetamido]benzoxazole derivatives, in continuing our efforts to enhance the antibacterial activity

against Gram-positive and Gram-negative bacteria and the antifungal activity against *C. albicans*, *C. glabrata*, and *C. krusei* of the benzoxazoles, we put a heterocyclic ring system instead of phenyl to the acetamido moiety on the C-5 position of benzoxazole.

All the newly synthesized compounds **3–14** showed some antibacterial activity against the Gram-positive bacteria such as *S. aureus* and *B. subtilis* possessing MIC values between 25 and 100 µg/mL as given in Table 1. Comparing the newly prepared compounds to previously synthesized compounds it was found that if the heterocyclic ring was attached to the acetamido moiety at the C-5 position of

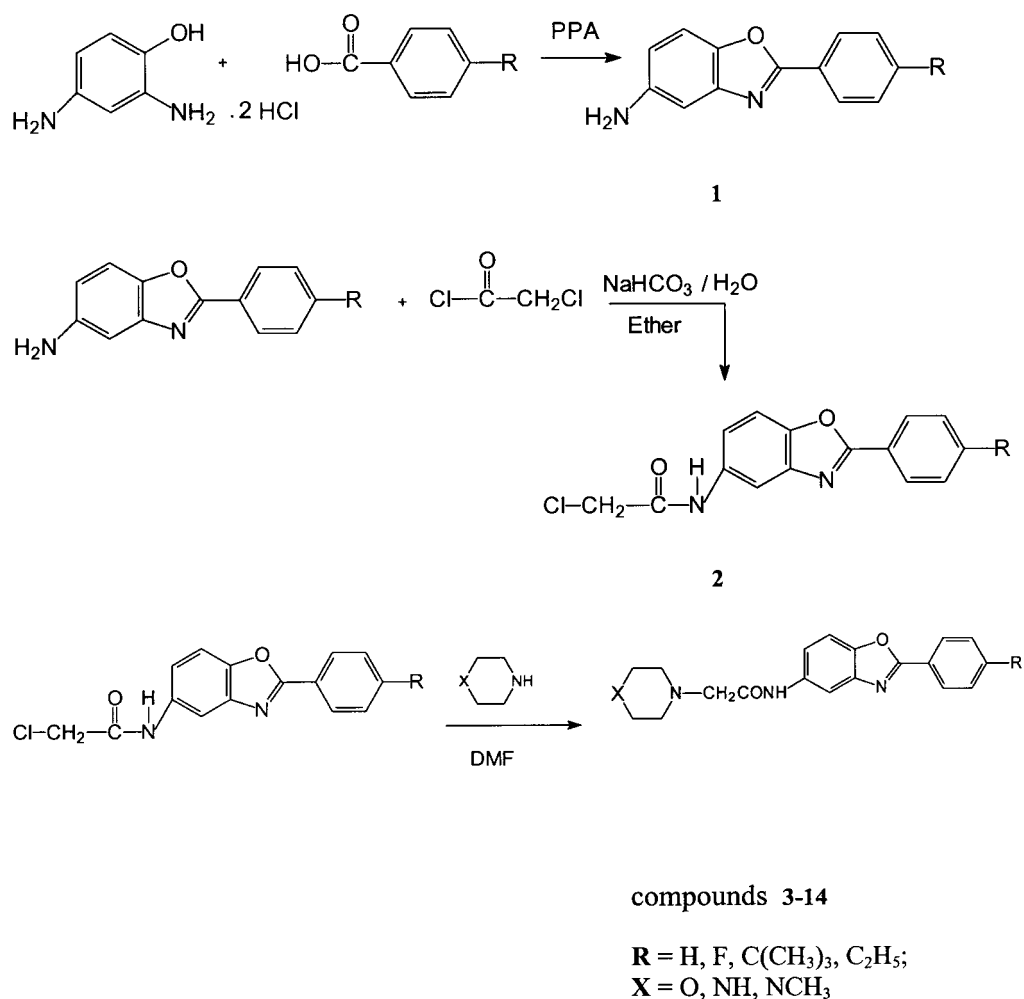
Table 2. Physicochemical properties and spectral data of the compounds **3–14**.



Comp.	R	X	Formula	Mp. [°C]	Yield [%]	IR [cm ⁻¹]	¹ H-NMR [δ ppm]	Mass [m/e]
3	-C ₂ H ₅	O	C ₂₁ H ₂₃ N ₃ O ₃	153	27	3300–2819, 1672, 1612, 1580–1527, 1484, 1271–1016	1.35 (t, 3H), 2.81–2.90 (6H), 3.32 (s, 2H), 3.84 (s, 4H), 7.57–7.72 (m, 4H), 8.12 (s, 1H), 8.20–8.31 (d, 2H), 9.35(1H)	365 (M ⁺), 98 (%100)
4	-C ₂ H ₅	NCH ₃	C ₂₂ H ₂₆ N ₄ O ₂	138	68	3282–2805, 1682, 1610, 1580–1500, 1481, 1299–1016	0.99–1.04 (t, 3H), 1.40–1.48 (m, 2H), 2.61 (s, 3H), 2.86–2.96 (8H), 3.37 (s, 2H), 7.49–7.51 (m, 4H), 8.13 (s, 1H), 8.29–8.31(d, 2H), 9.18 (s, 1H)	378 (M ⁺), 113 (%100)
5	-C ₂ H ₅	NH	C ₂₁ H ₂₄ N ₄ O ₂	140	35	3290–2800, 1681, 1620, 1540, 1480, 1285–1020	1.2–1.3 (s, 3H), 2.4–2.5 (6H), 2.7–2.8 (5H), 3.1 (s, 2H), 7.5–7.7 (m, 4H), 8.1–8.2 (m, 3H), 9.85 (s, 1H)	364 (M ⁺), 99 (%100)
6	-H	O	C ₁₉ H ₁₈ N ₃ O ₃	196	40	3300–2818, 1672, 1555, 1526, 1483, 1270–1052	2.86 (s, 4H), 3.39 (s, 2H), 3.98 (s, 4H), 7.66–7.71 (m, 5H), 8.2 (s, 1H), 8.38–8.40 (m, 2H), 9.80 (1H)	337 (M ⁺), 99 (%100)
7	-H	NCH ₃	C ₂₀ H ₂₁ N ₄ O ₂	135	25	3272–2800, 1681, 1556, 1585–1525, 1482, 1297–1015	2.57 (s, 3H), 2.79–2.91 (8H), 3.36 (s, 2H), 7.66–7.73 (m, 5H), 8.16 (d, 1H), 8.38–8.40 (m, 2H), 9.37 (s, 1H)	350 (M ⁺), 113 (%100)
8	-H	NH	C ₁₉ H ₁₉ N ₄ O ₂	156	30	3299–2819, 1672, 1555, 1526, 1482, 1273–1024	2.96 (s, 1H), 3.32–3.40 (8H), 3.55 (s, 2H), 7.41–7.69 (m, 5H), 8.19 (d, 1H), 8.38–8.41 (m, 2H), 9.23 (s, 1H)	335 (M ⁺), 99 (%100)
9	-F	O	C ₁₉ H ₁₇ N ₃ O ₃ F	179	67	3432–2852, 1683, 1605, 1530, 1484, 1275–1011, 852	2.68–2.70 (t, 4H), 3.22 (s, 2H), 3.82–3.84 (t, 4H), 7.21–7.55 (m, 4H), 8.05 (s, 1H), 8.25–8.28 (m, 2H), 9.23 (s, 1H)	355 (M ⁺), 99 (%100)
10	-F	NCH ₃	C ₂₀ H ₂₀ N ₄ O ₂ F	149	25	3343–2800, 1662, 1624, 1582, 1499, 1116–1011, 814	2.48 (s, 3H), 2.73–2.82 (8H), 3.25 (s, 2H), 7.21–7.59 (m, 4H), 8.02 (d, 1H), 8.25–8.28 (m, 2H), 9.20 (s, 1H)	368 (M ⁺), 113 (%100)

Table 2. (continued).

Comp.	R	X	Formula	Mp. [°C]	Yield [%]	IR [cm ⁻¹]	¹ H-NMR [δ ppm]	Mass [m/e]
11	-F	NH	C ₁₉ H ₁₈ N ₄ O ₂ F	176	30	3320-2828, 1676, 1605, 1562, 1486, 1290-1014, 855	3.05 (s, 1H), 3.35- 3.55 (8H), 3.91 (s, 2H), 7.34-7.69 (m, 4H), 8.16 (d, 1H), 8.37-8.41 (m, 2H), 9.11 (s, 1H)	354 (M ⁺), 99 (%100)
12	-C(CH ₃) ₃	O	C ₂₃ H ₂₇ N ₃ O ₃	227	40	3290-2800, 1681, 1620, 1540, 1480, 1285-1020	1.25 (s, 9H), 2.5-2.6 (4H), 3.2 (s, 2H), 3.3- 3.40 (4H), 3.6 (s, 1H), 7.6-7.8 (m, 4H), 8.1- 8.2 (m, 3H), 9.9 (s, 1H)	393 (M ⁺), 100 (%100)
13	-C(CH ₃) ₃	NCH ₃	C ₂₄ H ₃₀ N ₄ O ₂	178	30	3200-2830, 1676, 1550, 1530, 1480, 1280-1042	1.35 (s, 9H), 2.1-2.2 (s, 3H), 2.5 (8H), 3.15 (s, 2H), 7.55-7.75 (m, 4H), 8.1-8.2 (m, 3H), 9.9 (s, 1H)	406 (M ⁺), 113 (%100)
14	-C(CH ₃) ₃	NH	C ₂₃ H ₂₈ N ₄ O ₂	212	37	3386-2840, 1680, 1596, 1560, 1492, 1250-1100	1.25 (s, 9H), 2.4-2.6 (7H), 2.84- 2.90 (4H), 7.52-7.72 (m, 4H), 8.06-8.16 (m, 3H), 9.9 (s, 1H)	392 (M ⁺), 99 (%100)

**Scheme 1.** Synthetic pathway to get 5-(substituted-acetamido)benzoxazole derivatives 3–14.

benzoxazole, the antibacterial activity pretty much increased against *S. aureus* and *B. subtilis*. Interestingly, the activity decreased when nonsubstituted-piperazine was attached to the acetamido of position 5 of 2-phenylbenzoxazole.

Furthermore, the antibacterial activity of compounds **3–14** against *E. coli* as Gram-negative bacteria indicated a MIC value of 50 µg/mL. However, all the new compounds showed lower antibacterial activity than the standard drugs against the screened Gram-positive or Gram-negative bacteria. It should be considered that 4-propyloxyphenyl (comp. **19**) or 2-chlorophenyl (comp. **23**) groups attached to acetamido on the C-5 position of benzoxazole could enhance the activity against *E. coli* as demonstrated in Table 1.

On the other side, all compounds **3–23** showed notable activity against *C. albicans*, *C. krusei*, and *C. glabrata* with MIC values of 3.12–50 µg/mL. There were no significant results when the role of the substitution on acetamido group on C-5 of benzoxazole for *C. albicans* was considered. Furthermore, compounds **4**, **13**, and **14** were found to be more active against *C. glabrata* than the others with a MIC value of 12.5 µg/mL. Moreover, compound **13** was also the most active among the compounds having a MIC value of 3.12 µg/mL against *C. krusei*. Noteworthy, compound **13** was found to be one dilution less active than the compared drug, mycanazol. The compounds **5** and **12** were also very active ones in these series against *C. krusei* with a MIC value of 6.25 µg/mL. The SAR of the synthesized compounds revealed that those possessing a *p*-*tert*-butyl substituent of phenyl ring at the C-2 position of benzoxazole came up with the enhancing antifungal activity against *C. krusei* and *C. glabrata*. Consequently, for developing new antifungal agents against *C. krusei*, compound **13** could be the lead for further studies.

Acknowledgments

We thank the Research Fund of Ankara University (Grant No. 2001-08-03-27) for the financial support of this research.

Experimental

Chemistry

Silicagel HF₂₅₄ chromatoplates (0.3 mm; Merck, Darmstadt, Germany) were used for TLC. The solvent systems were chloroform:methanol (10:1) for compounds **3**, **6**, **9**, **12**; chloroform:2-propanol:ammonia (10:5:0.3) for compounds **7**, **10**, **13**, **14**; chloroform:2-propanol: ammonia (10:3:0.3) for compounds **4**, **5**, **8**, **11**. Melting points were taken on a Büchi SMP 20 capillary apparatus (Büchi Labortechnik, Flawil, Switzerland) and are uncorrected. IR spectra were recorded by FT/IR–420 in KBr discs (Shimadzu IR-470 spectrometer, Jasco, Tokyo, Japan). ¹H NMR spectra were ob-

tained with a Bruker DPX-400 High Performance Digital FT-NMR spectrometer (Bruker, Rheinstetten, Germany) in *d*-chloroform; tetramethylsilan (TMS) was used as an internal standard. MASS spectra were recorded by Micromass UK Platform II LC-MS (Micromass, Manchester, UK). Elemental analyses were carried out with a LECO CHN 932 analyzer (Leco, St. Joseph, MI, USA). The results (C, H, N) were within ± 0.4% of the calculated values.

General procedure for the synthesis of 5-amino-2-(*p*-substituted phenyl) benzoxazoles (**1**)

5-Amino-2-phenylbenzoxazole, 5-amino-2-(*p*-ethylphenyl)benzoxazole, 5-amino-2-(*p*-*tert*-butylphenyl)benzoxazole and 5-amino-2-(*p*-fluorophenyl) benzoxazole were synthesized by heating 0.01 mol 2,4-diaminophenol.2 HCl with 0.01 mol benzoic acid, *p*-ethylbenzoic acid, *p*-*tert*-butylbenzoic acid and *p*-fluorobenzoic acid in 24 g polyphosphoric acid with stirring for 2.5 h. At the end of the reaction period, the residue was poured into ice-water mixture and neutralized with an 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 the solvent *in vacuo*, the crude product was obtained and recrystallized [31].

General procedure for amide derivatives (**2**)

Chloroacetyl chlorid (0.04 mol) was added over a period of 1 h to a stirred, ice-cooled mixture of 5-amino-2-(*p*-substituted phenyl)-benzoxazoles (0.04 mol), sodiumbicarbonate (0.04 mol), diethylether (80 mL), and water (40 mL). The mixture was continuously stirred overnight at room temperature and filtered. The precipitate was washed with water, 2N HCl, water, respectively and finally with ether to give **2**. The product was recrystallized from ethanol-water mixture and needles were dried *in vacuo* [31].

General procedure for 5-[2-(morpholin-4-yl)acetamido]-2-(*p*-substituted phenyl)benzoxazoles (**2**)

The mixture of amide derivatives (3 mmol) and morpholine (3 mmol) in DMF (0.2 mL) was stirred and heated at 60 °C for 4 h. The reaction mixture was poured into ice-water, then, was made alkaline with 4N NaOH and saturated with NaCl. It was extracted with CHCl₃, the organic layer was dried with Na₂SO₄ and evaporated. The products were crystallized with ethanol and were dried *in vacuo*.

General procedure for 5-[2-(4-substituted piperazin-1-yl)acetamido]-2-(*p*-substituted phenyl)benzoxazoles (**3–14**)

2 mmol amide derivatives in 3 mL DMF were added to 3 mmol 1-substituted piperazine and 6 mmol triethylamine solutions in 2 mL DMF. The mixture was stirred at room temperature for 24 h. At the end of the reaction time, the mixture was poured into ice-water and the precipitate formed was filtered. Purification by flash chromatography: silica-gel column from appropriate solvents.

Microbiological assays

For 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, 0.78 µg/mL concentrations with Mueller-Hinton broth and Sabouraud dextrose broth. The minimum inhibitory concentrations (MIC) were determined using the twofold serial dilution technique [35, 36]. A control test was also performed containing inoculated broth supplemented with ethanol only at the same dilutions used in

our experiments and found inactive in the culture medium. All the compounds were tested for their *in vitro* growth inhibitory activity against different bacteria and the yeasts *Candida albicans* ATCC 10145, *Candida krusei* ATCC 6258, *Candida glabrata* (isolated). The origins of bacterial strains are *Staphylococcus aureus* ATCC 24923, *Bacillus subtilis* ATCC 6633 as Gram-positive and *Escherichia coli* ATCC 23556 as Gram-negative bacteria. ATCC 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.

Ciprofloxacin, gentamycin, oxiconazole, haloprogin, and miconazole were used as control drugs. The data on the antimicrobial activity of the compounds and the control drugs are given as MIC, µg/mL values in Table 1.

Antibacterial and antifungal assay

The cultures were obtained from Mueller-Hinton broth (Difco, Detroit, MI, USA) for all the bacterial strains after 24 h of incubation at $37 \pm 1^\circ\text{C}$. *Candida albicans*, *Candida krusei*, and *Candida glabrata* were maintained in Sabouraud dextrose broth (Difco) after incubation for 24 h at $25 \pm 1^\circ\text{C}$. Testing was carried out in Mueller-Hinton broth and Sabouraud dextrose broth (Difco) at pH 7.4 and the twofold 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 $37 \pm 1^\circ\text{C}$ and after incubation for 48 h at $25 \pm 1^\circ\text{C}$ 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.

References

- [1] R. Norrby, *Exp. Opin. Pharmacother.* **2001**, 2, 293–302.
- [2] A. N. Tomasz, *Engl. J. Med.* **1994**, 330, 1247–1251.
- [3] T. Hisano, M. Ichikawa, K. Tsumoto, M. Tasaki, *Chem. Pharm. Bull.* **1982**, 30, 2996–3004.
- [4] M. Prudhomme, J. Guyot, G. Jeminet, *J. Antibiotics* **1986**, 39, 934–937.
- [5] S. Ersan, S. Nacak, R. Berkem, T. Özden, *Arzneim. Forsch.* **1997**, 47, 963–965.
- [6] H. M. El-Shaar, S. A. Abdel-Aziz, H. A. Allimony, R. M. Abdel-Rahman, *Pharmazie* **1997**, 52, 585–589.
- [7] M. A. Weidner-Wells, K. A. Ohemeng, V. N. Nguyen, S. Fraga-Spano, M. J. Macielag, H. M. Werblood, B. D. Foleno, G. C. Webb, J. F. Barrett, D. J. Hlasta, *Bioorg. Med. Chem. Lett.* **2001**, 11, 1545–1548.
- [8] E. Şener, İ. Yalçın, E. Sungur, *Quant. Struc. Act. Relat.* **1991**, 10, 223–228.
- [9] E. Şener, İ. Yalçın, Ö. Temiz, İ. Ören, A. Akın, N. Uçartürk, *Farmaco* **1996**, 52, 99–103.
- [10] İ. Ören, Ö. Temiz, İ. Yalçın, E. Şener, A. Akın, N. Uçartürk, *Arzneim. Forsch.* **1997**, 47, 1393–1397.
- [11] Ö. Temiz, İ. Ören, E. Şener, İ. Yalçın, N. Uçartürk, *Farmaco* **1998**, 53, 337–341.
- [12] İ. Yalçın, İ. Ören, E. Şener, A. Akın, N. Uçartürk, *Eur. J. Med. Chem.* **1992**, 27, 401–406.
- [13] J. Kogi, V. Klimegova, K. Waissner, J. Kaustava, H. M. Dahse, U. Möllmann, *Bioorg. Med. Chem. Letters*, **2002**, 12, 3275–3278.
- [14] M. Ueki, K. Ueno, S. Miyadoh, K. Abe, K. Shibata, M. Taniguchi, *J. Antibiotics* **1993**, 46, 1089–1094.
- [15] D. F. Shi, T. D. Bradshaw, S. Wrigley, C. J. McCall, P. Lelieveld, I. Fichtner, M. F. G. Stevens, *J. Med. Chem.* **1996**, 39, 3375–3384.
- [16] M. DeLuca, S. Kerwin, *Tetrahedron Letters* **1997**, 38, 199–202.
- [17] M. B. Reynolds, M. DeLuca, S. Kerwin, *Bioorg. Chem.* **1999**, 27, 326–337.
- [18] Z. M. Nofal, M. El-Zahar, S. S. Abd El-Karim, *Molecules* **2000**, 5, 99–153.
- [19] S. Sato, T. Kajiura, M. Noguchi, K. Takehana, T. Kobayashi, T. Tsuji, *J. Antibiotics* **2001**, 54, 102–104.
- [20] W. S. Saari, J. S. Wai, T. E. Fisher, C. M. Thomas, J. M. Hoffman, C. S. Roomey, A. M. Smith, J. H. Jones, D. L. Bamberger, M. E. Goldman, J. A. O'Brien, J. H. Nunberg, J. C. Quintero, Q. A. Schleif, E. A. Emini, P. S. Anderson, *J. Med. Chem.* **1992**, 35, 3792–3802.
- [21] M. E. Goldman, J. A. O'Brien, T. L. Ruffing, W. A. Schleif, V. V. Sardana, V. W. Byrnes, J. H. Condra, J. M. Hoffman, E. A. Emini, *Antimicrob. Agents Chemother.* **1993**, 37, 947–949.
- [22] J. M. Hoffman, A. M. Smith, C. S. Rooney, T. E. Fisher, J. S. Wai, C. M. Thomas, D. L. Bamberger, J. L. Barnes, T. M. Williams, J. H. Jones, B. D. Olson, J. A. O'Brien, M. E. Goldman, J. H. Nunberg, J. C. Quintero, W. A. Schleif, E. A. Emini, P. S. Anderson, *J. Med. Chem.* **1993**, 36, 953–966.
- [23] R. T. Davey, R. L. Dewar, G. F. Reed, M. B. Vasudevachari, M. A. Polis, J. A. Kovacs, J. Falloon, R. E. Walker, H. Masur, S. E. Haneiwich, D. G. O'Neil, M. R. Decker, J. A. Metcalf, M. A. Deloria, O. L. Laskin, N. Salzman, H. C. Lone, *Proc. Natl. Acad. Sci. U.S.A.* **1993**, 90, 5608–5612.
- [24] S. Staszewski, F. E. Massari, A. Kober, R. Göhler, S. Durr, K. W. Anderson, C. L. Schneider, J. A. Waterbury, K. K. Bakshi, V. I. Taylor, *J. Infect. Dis.* **1995**, 171, 1159–1165.
- [25] D. B. Olsen, S. S. Carroll, J. C. Culbertson, J. A. Shafer, L. C. Kuo, *Nucleic Acids Res.* **1994**, 22, 1437–1443.
- [26] W. Dolbier, C. Burkholder, M. Medebielle, *J. Fluor. Chem.* **1999**, 95, 127–130.
- [27] J. S. Kim, Q. Sun, B. Gatto, C. Yu, A. Liu, L. F. Liu, E. J. La Voie, *Bioorg. Med. Chem.* **1996**, 4, 621–630.
- [28] M. Peel, M. Milstead, D. Sternbach, J. Besterman, P. Leitner, B. Morton, M. Wall, M. Wani, *Bioorg. Med. Chem. Lett.* **1995**, 5, 2129–2131.
- [29] D. Kumar, M. R. Jacob, M. B. Reynolds, S. M. Kerwin, *Bioorg. Med. Chem.*, **2002**, 10, 3997–4004.
- [30] D. D. Martin, N. R. Kotecha, S. V. Ley, S. Maqtegan, J. C. Menendes, H. M. Organ, A. D. White, *Tetrahedron* **1992**, 48, 7899–7938.
- [31] E. A. Sener, Ö. T. Arpacı, İ. Yalçın, N. Altanlar, N., *Il Farmaco* **2000**, 55, 397–405.
- [32] Ö. T. Arpacı, E. A. Sener, İ. Yalçın, N. Altanlar, *Arch. Pharm. Pharm. Med. Chem.* **2002**, 335, 283–288.
- [33] İ. Yalçın, B. K. Kaymakcioğlu, İ. Ören, E. Şener, Ö. Temiz, A. Akın, N. Altanlar, *Il Farmaco* **1997**, 52, 685–689.
- [34] L. E. Totton, C. L. Raiford, *J. Am. Chem. Soc.* **1954**, 76, 5127–5130.
- [35] E. S. Charles, V. K. Agrawal, S. Sharma, R. N. Iyer, *Eur. J. Med. Chem., Chim. Ther.* **1979**, 4, 435–438.
- [36] S. Shadomy, A. Espinel in *Manual of clinical microbiology* (Ed.: E. H. Lennette), Am. Soc. Microbiol, Washington, DC, **1980**, pp. 647.