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# SYNTHESIS AND STRUCTURE-ACTIVITY RELATIONSHIPS OF SOME 2,5-DISUBSTITUTED BENZOXAZOLES AND BENZIMIDAZOLES AS ANTIMICROBIAL AGENTS

ESİN ŞENER, İSMAİL YALÇIN (*), ÖZLEM TEMİZ and İLKAY ÖREN
*Ankara University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry; 06100 Tandoğan, Ankara, Turkey*

AHMET AKIN and NEJAT UÇARTÜRK
*Ankara University, Faculty of Pharmacy, Department of Microbiology, 06100 Tandoğan, Ankara, Turkey*

*Summary* – The synthesis of a new series of 2,5-disubstitutedbenzoxazoles **5a-e**, and 2,5-disubstituted-benzimidazoles **6a-h** are described in order to determine their antimicrobial activities and feasible structure-activity relationships (SAR). The synthesized compounds were tested in vitro against 3 Gram-positive, 3 Gram-negative, bacteria and a fungus *Candida albicans*. **5c**, and **5e** were found most active than the others against *Bacillus subtilis* at a MIC value of 3.12 μg/ml and the compounds **5e**, **6a** and **6e** indicated significant antibacterial activity against the enterobacter *Pseudomonas aeruginosae*. **5a**, **5c**, **5d** and **6d** also exhibited antimycotic activity against *C. albicans*. The antibacterial and antimycotic activities of **5-6** are compared with several control drugs.

## INTRODUCTION

Benzoxazole and benzimidazole derivatives are the structural isosters of naturally occurring nucleotides, which allow them to interact easily with the biopolymers of the living systems and different kinds of biological activity have been obtained.

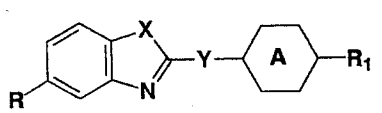
Recently, the antimicrobial effect of benzimidazoles has been studied extensively. Particularly, substituted 2-aminobenzimidazole[1] derivatives have received much attention. In addition, carbamate derivatives of the 2- aminobenzimidazoles[2] have been synthesized for their significant *in vivo* antifilarial activity. A series of 2-(2-hydroxyphenyl)benzimidazoles[3] were prepared as potential agents for the control of periodontitis against *Actinomyces viscosus* and *Bacteriodes gengivalis*. Pyrimido[1,6-a]benzimidazoles[4] have been developed as a new class of inhibitors of DNA gyrase and their synthesis and potent antibacterial activity were reported. Jung *et al.*[5] have synthesized new cephalosporin derivatives which possess an aminobenzimidazole ring at their structure. On the other side, the influence of the substitution of the position 1[6], 2[1,2,6-12] and 5(6)[4,7,11,12] on the benzimidazole ring for the antimicrobial activity are well known and various heterocycles linked to benzimidazole and benzoxazole rings[4,13-17] provided some potent antimicrobial compounds.

2-substituted benzoxazoles were also prominently studied[18-26], trusting that this position is decisive for the biological activity, whereas position 5[20,22,26,27] is prevailing for the intensity of activity. It was reported[20,21] that para substituted 2-aryl-5-benzoxazolealkanoic acid derivatives had the highest activity compared to analogues. Benoxaprofen[19,22] and Zoxazolamin[22] are examples of benzoxazole derivatives which are substituted at both 2 and 5 positions.

Calcimycin (A 23187) which is an antibiotic isolated from a strain of *Streptomyces chartreusis* (NRRL 3882), encludes a benzoxazole ring in its molecular structure[28]. Calcimycin was found very active against *Bacillus cereaus, Bacillus megaterium,* and *Micrococcus lutes*.

In the last few years we described the synthesis of different derivatives of 5-substituted-2-(p-substitutedphenyl)benzoxazoles, 5-substituted-2-(p-substitutedbenzyl)benzoxazoles, 5-substituted-2-(2-cyclohexylethyl) benzoxazoles and 2-(2-cyclohexylethyl)benzimidazoles (**1-4**), and the results of assays on their *in vitro* antimicrobial activity against some Gram-positive, Gram-negative bacteria and the fungus *Candida albicans*[29-32].

SCHEME 1




**1** X = OY = – A = Phenyl R = H, Cl, $NO_2$, $NH_2$, $CH_3$ $R_1$ = H, $CH_3$, $C_2H_5$, F, Br, Cl, $NHCH_3$, $NO_2$, $NH_2$, $C(CH_3)_3$, $NHCOCH_3$, $NH(CH_3)_2$, $OCH_3$
**2** X = OY = $CH_2$ A = Phenyl R = H, Cl, $NO_2$, $CH_3$ $R_1$ = H, $OCH_3$, Cl, Br, $NO_2$
**3** X = OY = $C_2H_4$ A = Phenyl or Cyclohexyl R = H, Cl, $NO_2$, $NH_2$ $R_1$ = H
**4** X= NH Y= $C_2H_4$ A = Phenyl or Cyclohexyl R = $R_1$ = H

In the present paper, the syntheses of new series of compounds **5a-e** and **6a-h**, including two isosteric heterocyclic nuclei, as well as their *in vitro* antibacterial and antimycotic activities are described and the feasible structure-activity relationships (SAR) of the target structures **5-6** are also examined.

(*) To whom correspondence should be addressed.

## CHEMISTRY

The synthesis of the compounds 2,5-disubstituted-benzoxazoles **5** and benzimidazoles **6** were performed through heating carboxylic acids with appropriate o-substituted anilines by means of several dehydrating agents in a one-step procedure.

Polyphosphate esters (PPE)[29,33,34] was used as the cyclodehydration reagent in the synthesis of compounds **5a-e**.

During the synthesis of **6a-h**, aqueous hydrochloric acid was used as the condensation reagent, according to the well-known Phillip's method[35].

Compounds **5-6** were prepared as new products except **5a**[36], **6a**[37], **6c**[38], and **6e**[39]. The structures of all the derivatives **5a-e** and **6a-h** 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 I.

## EXPERIMENTAL

### A) CHEMISTRY

Kieselgel $HF_{254}$ chromatoplates (0.3 mm) were used for TLC and the solvent systems were chloroform: methanol (30:5) for compounds **5a-e** chloroform: acetone (10:2) for compounds **6a-h**. All melting points were taken on a Buchi SMP 20 capillary apparatus and uncorrected. IR spectra were recorded by Pye Unicam SP-1025 with KBr discs. $^1$H NMR spectra were obtained with a Bruker 80 MHz spectrometer in $d_6$-chloroform and 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 analysis (C, H, N) were within ±0.4% of the calculated amounts.

The compounds were prepared by three general methods which differed according to the dehydrating agent used. The cyclodehydration reagent PPE[34] was prepared in our laboratory by the method described in. Data on the preparation of the compounds are summarized in Table I. The reaction mixtures were protected from moist air by means of a calcium chloride drying tube and stirred magnetically. The starting compounds and the solvents were commercially available products.

### PREPARATION OF PPE

A mixture of $P_4O_{10}$ (150 g), chloroform (300 ml), and absolute ether (150 ml) were heated to boiling point in a flask under reflux using a heating mantle of 60-65 °C for 30 h. After pentoxide was dissolved completely in the reaction, the mixture was filtered through glass wool and any excess of the solvent was removed in a rotary evaporator. The residue was obtained to give PPE as a viscous, colorless to yellowish substance which forms a stiff gel below 0 °C.

### GENERAL PROCEDURE FOR 5-SUBSTITUTED-2-CYCLOHEXYL AND/OR 2-CYCLOHEXYLMETHYL-BENZOXAZOLES **5a,b,c,d, e** (METHOD A)

A mixture of 2-hydroxy-5-substitutedaniline **7** (0.01 mol) and cyclohexylcarboxylic acid **9** or 2-cyclohexylacetic acid **10** (0.015 mol) was heated at bath-temperature in PPE (10 g). At the end of the reaction period, the mixture was poured into ice-water and neutralized with an excess of $NaHCO_3$. After being extracted with benzene the combined benzene extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo*. The crude product was obtained and recrystallized.

### GENERAL PROCEDURE FOR 5-SUBSTITUTED-2-CYCLOHEXYL AND/OR 2-CYCLOHEXYLMETHYL-BENZIMIDAZOLES **6a,b,c,d,e,f,g,h** (METHOD B)

A mixture of p-substituted-o-phenylenediamine **8** (0.01 mol), **9** or **10** (0.015 mol) and 4 N HCl (10 ml) were boiled under reflux. At the end of the reaction period, the reaction mixture was poured into ice-water and neutralized with excess of $NaHCO_3$. The precipitate was collected, washed, dried and extracted with benzene to separate from impurities. After the evaporation of solvent *in vacuo*, the crude product was obtained and recrystallized.

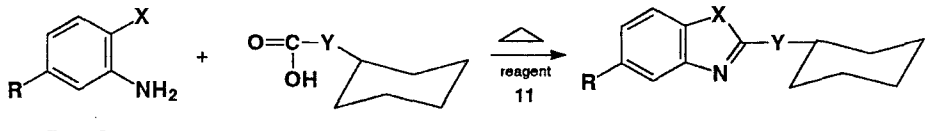
### B) MICROBIOLOGY

For both the antibacterial and the antimycotic assays, the compounds were dissolved in absolute ethanol (0.8 mg/ml)[40]. Further dilutions of the compounds and standard drugs in the test medium were furnished at the required quantities of 400, 200, 100, 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78 µg/ml concentrations. The minimum inhibitory concentrations (MIC) were determined using the method of two-fold serial dilution technique[29,40,41]. In order to ensure that the solvent per se had no effect on bacterial growth, a control test was also performed containing inoculated broth supplemented with only ethanol at the same dilutions used in our experiments and found inactive in culture medium.

All the compounds were tested for their *in vitro* growth inhibitory activity against different bacteria and a fungus *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, *Klepsiella pneumoniae NTCC* 52211, 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, gentamycin, streptomycin, oxiconazole, and haloprogin were used as control drugs. The observed data on the antimicrobial activity of the compounds and the control drugs are given in Table II.

SCHEME 2



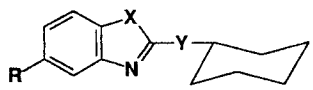

**7** or **8** **9** or **10** **5** or **6**

Method A
**7** X = OH, R= H, Cl, $NO_2$
**9** Y = –
**10** Y = $CH_2$
**11** PPE

Method B
**8** X = $NH_2$, R= H, Cl, $NO_2$, $CH_3$
**9** Y = –
**10** Y = $CH_2$
**11** 4 N HCl

**5** X = O Y = –, $CH_2$ R = H, Cl, $NO_2$
**6** X = NH Y = –, $CH_2$ R = H, Cl, $NO_2$, $CH_3$

TABLE I - Physical properties, preparation and spectral data of the compounds **5-6**



| Comp. | R | X | Y | Reaction time (h) | Reaction temp. (°C) | Method | Cryst. sol.* | m.p. (°C) | Yield (%) | IR ($cm^{-1}$) | $^1H$ NMR δ ppm (J = Hz) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **5a** | H | O | - | 2.5 | 80-90 | A | a | 39.5 | 25 | 3100, 2995, 1630, 1580, 1470, 1260 | 7.73-7.20 (4H,m), 2.19-1.35 (11H,m) |
| **5b** | Cl | O | - | 3 | 85-90 | A | a | 52.5 | 21 | 3100, 2750, 1600, 1550,1440, 1250 | 7.80-6.90 (3H,m), 2.50-1.00 (11H,m) |
| **5c** | $NO_2$ | O | - | 3.5 | 90 | A | a | 69.5 | 16 | 3090, 2980, 1620, 1540, 1355, 1455,1255 | 8.65-7.95 (2H,m),7.55 (1H,d; $J_{7,6}$=8), 2.50-0.70 (11H,m) |
| **5d** | Cl | O | $CH_2$ | 2.5 | 95-100 | A | a | 27.5 | 53 | 3100, 2920, 1600, 1570,1450, 1250 | 7.75-6.75 (3H,m),2.25 (2H,d; J= 6.75), 2.05-0.75 (11H,m) |
| **5e** | $NO_2$ | O | $CH_2$ | 3 | 100-110 | A | a | 68.5 | 31 | 3120, 2980, 1620, 1580, 1540, 1460,1360, 1240 | 8.70-8.10 (2H,m),7.60 (1H,d; $J_{7,6}$= 10), 2.85 (2H,d; J=7.11) 2.30-0.72 (11H,m) |
| **6a** | H | NH | - | 15 | 100 | B | b | 190 | 10 | 3100, 2960, 1630, 1600, 1540, 1460,1270 | 7.62-7.51(2H,m),7.20-6.64(2H,m), 2.22-1.80(11H,m) |
| **6b** | Cl | NH | - | 15 | 100 | B | a | 232 | 51 | 3100,3000,1610, 1570, 1520, 1440,1280 | 7.16-7.03(1H,dd; $J_{6,7}$=8.4;$J_{6,4}$=2),7.49-7.38(2H,m), 2.06-1.52(11H,m) |
| **6c** | $NO_2$ | NH | - | 15 | 90-100 | B | a | 206 | 61 | 3100, 2960, 1640, 1600, 1540, 1450,1350,1260 | 8.45-8.42(1H,d;$J_{4,6}$=2.16),8.16-8.03(1H,dd;$J_{6,7}$=8.8; $J_{6,4}$=2.24), 7.61-7.50(1H,d;$J_{7,6}$=8.8),2.29-1.48(11H,m) |
| **6d** | $CH_3$ | NH | - | 15 | 90-100 | B | a | 175 | 28 | 3095, 2940, 1640, 1560, 1450, 1280 | 8.78(1H,s),7.51-6.99(3H,m), 2.41(3H,s),1.85-1.67(11H,m) |
| **6e** | H | NH | $CH_2$ | 12 | 105 | B | b | 231 | 19 | 3095, 2920, 1630,1550, 1440,1270 | 7.70-6.97(4H,m),2.83-2.75(2H,d; J=6.95), 1.96-0.91(11H,m |
| **6f** | Cl | NH | $CH_2$ | 10 | 110 | B | a | 189.5 | 12 | 3100,2960,1630, 1550, 1450, 1230,1270 | 7.49-7.37(2H,m),7.15-7.02(1H,dd;$J_{6,7}$=8.56,$J_{6,4}$=1.92), 2.79-2.70(2H,d; J=6.88), 1.87-1.11(11H,m) |
| **6g** | $NO_2$ | NH | $CH_2$ | 6 | 110 | B | a | 167 | 15 | 3110, 2920, 1620, 1580, 1510, 1450,1330,1250 | 8.44-8.41(1H,d;$J_{4,6}$=2.24),8.17-8.03(1H,dd; $J_{6,7}$=8.96, $J_{6,4}$=2.16), 7.61-7.50(1H,d; $J_{7,6}$=8.8), 2.85-2.77 (1H,d;J=6.88), 2.58-1.04(11H,m) |
| **6h** | $CH_3$ | NH | $CH_2$ | 12 | 100-110 | B | a | 179 | 14 | 3120,2960,1640, 1550, 1460, 1280 | 7.62-7.15(3H,m),3.05-2.96(2H,d;J=7.2), 2.58(3H,s), 2.47-1.70(11H,m) |

(*) a: Ethanol-water, b: Benzene-petroleum ether.

TABLE II - The *in vitro* antimicrobial activity of the compounds **5-6** and the standart drugs (MIC in μg/ml)

| Comp. | Microorganisms[a] | | | | | | |
|---|---|---|---|---|---|---|---|
| | Gram-positive | | | Gram-negative | | | Fungus |
| | *Sa* | *Sf* | *Bs* | *Ec* | *Kp* | *Pa* | *Ca* |
| 5a | 50 | 50 | >200 | 50 | 25 | 50 | 12.5 |
| 5b | 25 | 50 | 50 | 50 | 25 | 25 | 50 |
| 5c | 25 | 25 | 3.12 | 25 | 25 | 25 | 12.5 |
| 5d | 25 | 50 | >200 | 50 | 25 | 50 | 12.5 |
| 5e | 50 | 50 | 3.12 | 25 | 25 | 12.5 | 50 |
| 6a | 50 | 50 | 6.25 | 25 | 12.5 | 12.5 | 25 |
| 6b | 25 | 50 | 25 | 50 | 25 | 25 | 50 |
| 6c | 25 | 50 | 25 | 50 | 25 | 25 | 50 |
| 6d | 50 | 50 | >200 | 50 | 12.5 | 25 | 12.5 |
| 6e | 25 | 25 | 6.25 | 25 | 25 | 12.5 | 25 |
| 6f | 25 | 50 | 12.5 | 50 | 25 | 25 | 25 |
| 6g | 12.5 | 50 | 25 | 50 | 25 | 50 | 50 |
| 6h | 25 | 50 | 25 | 50 | 25 | 25 | 50 |
| Ampicillin | 0.78 | 0.78 | 0.78 | 3.12 | 12.5 | >200 | - |
| Amoxycillin | 0.78 | 0.78 | 0.78 | 3.12 | 12.5 | >200 | - |
| Tetracycline | 0.78 | 0.78 | 0.78 | 3.12 | 3.12 | 50 | - |
| Gentamycin | 0.78 | 12.5 | 0.78 | 3.12 | 1.56 | 12.5 | - |
| Streptomycin | 3.12 | 100 | 50 | 1.56 | 1.56 | 100 | - |
| Oxiconazole | - | - | | - | - | - | 6.25 |
| Haloprogin | - | - | | - | - | - | 6.25 |

([a]) Abbreviations; *Sa, Staphylococcus aureus; Sf, Streptococcus faecalis; Bs, Bacillus subtilis; Ec, Escherichia coli; Kp, Klebsiella pneumoniae; Pa, Pseudomonas aeruginosa; Ca, Candida albicans.*

### 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. A set of tubes containing only inoculated broth was kept as controls. After incubation for 24 h at 37±1 °C, the last tube with no growth of microorganism was recorded to represent MIC expressed in µg/ml.

### ANTIMYCOTIC 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. 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.

## RESULTS AND DISCUSSION

In order to determine the antimicrobial activity of the synthesized compounds **5-6**, three Gram-positive, three Gram-negative bacterial strains and the fungus *C. albicans* were screened using two fold serial dilution technique. The results reported in table II indicate that compounds **5-6** are able to inhibit *in vitro* growth of a number of microorganisms having very different MIC values.

Synthesized compounds **5-6** provided low antibacterial activity against the screened Gram-positive bacteria *S. aureus* and *S. feacalis*, showing MIC values between 25-50 µg/ml with the exception of 5-nitro-2-cyclohexylmethylbenzimidazole (**6g**) possessing a MIC value of 12.5 µg/ml against *S. aureus*. For microorganism *B. subtilis*, the synthesized compounds indicated a wide range of MIC values. While the compounds **5a**, **5d** and **6d** proved lacking in activity, 5-nitro-2-cyclohexylbenzoxazole (**5c**) and 5-nitro-2-cyclohexylmethylbenzoxazole (**5e**) showed a very good activity, having MIC value 3.12 µg/ml. Moreover, most of the compounds (**5c, 5e, 6a-6c** and **6e-6h**) were found more active against *B. subtilis* than the other tested Gram-positive bacteria.

The activity of the compounds **5-6** were also tested against *E. coli*, *K. pneumoniae* and *P. aeruginosae* as Gram-negative bacteria and exhibited MIC values between 25-50 µg/ml against *E. coli* indicating lower potency than the compared control drugs. 2-Cyclohexylbenzimidazole (**6a**) and 5-methyl-2-cyclohexylbenzimidazole (**6d**) are more active than the other tested compounds showing 12.5 µg/ml MIC value against *K. pneumoniae*.

In the determination of the antibacterial activity against *P. aeruginosae* which is an enterobacter effective in nosocomial infections and often resistant to antibiotic therapy, the derivatives 5-nitro-2-cyclohexylmethylbenzoxazole (**5e**), 2-cyclohexylbenzimidazole (**6a**) and 2-cyclohexylmethylbenzimidazole (**6e**) exhibited significant activity having MIC values 12.5 µg/ml.

Moreover, synthesized compounds were tested against *C. albicans* for antimycotic activity and exhibited MIC values between 12.5-50 µg/ml. The derivatives 2-cyclohexylbenzoxazole (**5a**), 5-nitro-2-cyclohexylbenzoxazole (**5c**), 5-chloro-2-cyclohexylmethylbenzoxazole (**5d**) and 5-methyl-2-cyclohexylbenzimidazole (**6d**) were found more active than the other tested compounds having 12.5 µg/ml MIC values. However, antimycotic activity of the control drugs oxiconazole and haloprogin were observed one dilution better than the corresponding compounds showing 6.12 µg/ml MIC values.

In conclusion, the two different heterocyclic nuclei at the synthesized compounds indicate bioisosteric effects for the antimicrobial activity in the screened microorganisms. Substitution of position 2 on the heterocyclic ring with cyclohexyl or cyclohexylmethyl groups produces no difference in the activity. In some cases, holding a nitro group at the position 5 on the benzoxazole ring system increases the potency especially against *B. subtilis* and *P. aeruginosae*.

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