

## Structure-activity relationships of some antimicrobial 5-substituted 2-(3-pyridyl)benzoxazoles using quantum-chemical calculations

Esin Şener <sup>a,\*</sup>, Hülya Turgut <sup>a</sup>, İsmail Yalçın <sup>a</sup>, İlkey Ören <sup>a</sup>, Lemi Türker <sup>b</sup>,  
Nihat Çelebi <sup>b</sup>, Ahmet Akın <sup>c</sup>

<sup>a</sup> Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Ankara University, Tandoğan, 06100 Ankara, Turkey

<sup>b</sup> Department of Chemistry, Middle East Technical University, 06531 Ankara, Turkey

<sup>c</sup> Department of Microbiology, Faculty of Pharmacy, Ankara University, Tandoğan, 06100 Ankara, Turkey

(Received 13 December 1993; Accepted 28 February 1994)

### Abstract

The synthesis and in vitro antimicrobial activity of 5-substituted 2-(3-pyridyl)benzoxazoles (**3–7**) is described for some Gram-positive and Gram-negative bacteria and the yeast *Candida albicans*. The compounds **3–7** exhibited significant activity against the screened microorganisms, having MIC values between 25 and 12.5 µg/ml. Quantum-chemical calculations were performed for the compounds **1–10**, in order to observe some feasible structure-activity relationships. These theoretical observations, calculated for the description of the mechanism of interactions at the molecular level, revealed that the electrophilic superdelocalizability of the nitrogen atom ( $S_N^E$ ) in the oxazolo moiety of the benzoxazole ring is related to the activity. The results obtained from the theoretical calculations and the observed MIC values show that 2-(3-pyridyl)- and 2-phenylbenzoxazole derivatives exhibit bio-isosteric effects for antimicrobial activity. Additionally, substituents at position 5 on the fused heterocyclic system contribute to the activity constructively or destructively depending on the type of microorganism screened.

**Key words:** 5-Substituted 2-(3-pyridyl)benzoxazoles; Antibacterial activity; Antimycotic activity; Quantum-chemical calculations; Structure-activity relationship

### 1. Introduction

Recently, we have described the synthesis and microbiological activity of various 2,5-disubstituted benzoxazoles (Yalçın et al., 1990, 1992). The determination of the in vitro antibacterial

and antimycotic activities of the previously synthesized compounds indicated that some of the 5-substituted-2-phenylbenzoxazole derivatives were significantly active, especially against some Gram-negative rods (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*) and the yeast *Candida albicans*. In order to interpret the nature and the effects of the substituents, the developed quantitative structure-activity relationship (QSAR)

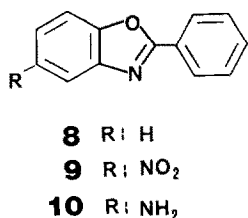
\* Corresponding author.

Fig. 1. Structures of compounds **1** and **2**.

analysis revealed that the substituents at positions 2 and 5 and/or the oxazolo ring in the fused heterocyclic system were important for the microbiological activity (Şener et al., 1991; Yalçın and Şener, 1993).

Hisano et al. (1982) synthesized the 2-(2-pyridyl)- and 2-(4-pyridyl)benzoxazoles (**1**, **2**) (Fig. 1) and stated that these compounds exhibited insignificant activity against *Bacillus subtilis*, *Ps. aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, and *Mycobacterium ovicum*. Although compounds **1** and **2** have previously been studied, the 2-(3-pyridyl)-substituted analog has not yet been screened for antimicrobial activity.

In this study, we prepared and examined the *in vitro* antimicrobial activity of some 5-substituted 2-(3-pyridyl)benzoxazole derivatives (**3–7**) (Scheme 1), in order to compare their effects with those of the previously synthesized compounds **1**, **2** and 5-substituted 2-phenylbenzoxazoles (**8–10**) (Fig. 2). The activity contributions of either 2-pyridyl- or 2-phenylbenzoxazoles and/or the substituents at position 5 in the tested compounds have been compared and the predictions for the description of the mechanism of interactions at the molecular level are described by using quantum-chemical calculations.

Fig. 2. Structures of compounds **8–10**.

## 2. Materials and methods

### 2.1. Synthesis of 5-substituted 2-(3-pyridyl)benzoxazoles (**3–7**).

Polyphosphoric acid (PPA) was used as the cyclodehydration reagent in the synthesis of compounds **3–7** as illustrated in Scheme 1 (Yalçın et al., 1990).

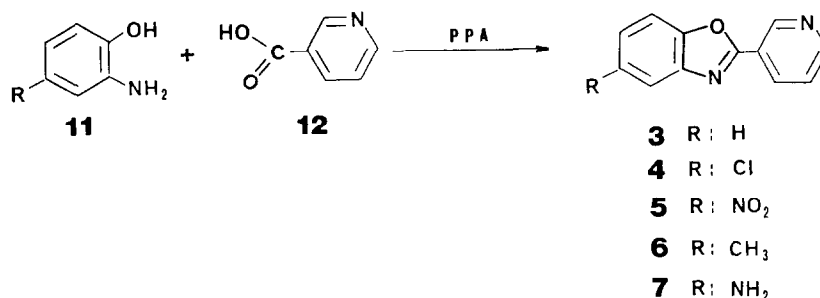
For the preparation of the compounds, a mixture of 2-hydroxyl-5-substituted anilines (**11**) (0.01 mol) and nicotinic acid (**12**) (0.015 mol) was heated in PPA (12 g) with stirring for 2 h. At the end of the reaction period, the residue was poured into ice-water and neutralized with an excess of 10% NaOH solution. After extraction with chloroform, the combined chloroform extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was crystallized using diethyl ether/petroleum ether (2:1).

The structures of the synthesized compounds were supported by elemental analyses and spectral data. The UV, IR, and <sup>1</sup>H-NMR spectra were consistent with the proposed structures. The chemical, physical and spectral data of compounds **3–7** are reported in Table 1.

Kieselgel HF<sub>254</sub> chromatoplates (0.3 mm) were used for TLC and the solvent system employed was chloroform/diethyl ether (5:1). All melting points were taken on a Buchi SMP 20 capillary apparatus and are uncorrected. IR spectra were recorded on a Pye Unicam SP-1025 instrument with KBr discs. <sup>1</sup>H-NMR spectra were obtained with a Bruker 80 MHz spectrometer in *d*-chloroform, TMS being used as an internal standard. UV maxima were measured on a Pye Unicam SP-1700 spectrophotometer in methanol at a concentration of 10<sup>-4</sup> M. Elemental analyses were carried out with a Perkin Elmer 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4% of the calculated amounts. The starting compounds and the solvents were commercially available products.

### 2.2. *In vitro* microbiological activity

The compounds were dissolved in absolute ethanol (0.2 mg/ml) for both the antibacterial



Scheme 1.

Table 1  
Physical properties, preparation and spectral data of the compounds 3–7 <sup>a</sup>

Compound no.	Reaction temperature (°C)	Yield (%)	m.p. <sup>b</sup> (°C)	UV		<sup>1</sup> H-NMR (δ, ppm) (J in Hz)	IR (cm <sup>-1</sup> )
				max	log ε		
<b>3</b>	120	55	108 <sup>c</sup>	213 229 <sup>f</sup> 294 <sup>f</sup> 302	4.14 4.06 4.37 4.38	9.47 (d, <i>J</i> = 1.94, 1H); 8.77 (dd, <i>J</i> = 6.32 and 1.57, 1H); 8.52 (dd, <i>J</i> = 7.98 and 1.57, 1H); 7.26–7.87 (m, 5H)	3040, 1615, 1545, 1195, 1020
<b>4</b>	150	52	153 <sup>d</sup>	217 306	4.26 4.29	9.46 (d, <i>J</i> = 1.68, 1H); 8.78 (dd, <i>J</i> = 6.23 and 1.42, 1H); 8.50 (dd, <i>J</i> = 8.14 and 1.42, 1H); 7.78 (d, <i>J</i> = 1.90, 1H); 7.25–7.61 (m, 3H)	3040, 1610, 1550, 1190, 1020
<b>5</b>	160	36	180	220 262	3.95 4.28	9.49 (s, 1H); 830– 8.70 (m, 4H); 7.54– 7.78 (m, 2H)	3080, 1610, 1550, 1520, 1350, 1260, 1050
<b>6</b>	150	63	102 <sup>c</sup>	211 230 <sup>f</sup> 307	4.06 3.83 4.27	9.46 (s, 1H); 8.41– 8.73 (m, 2H); 7.14– 7.65 (m, 4H); 2.49 (s, 3H)	3040, 2905, 2850, 1620, 1545, 1195, 1020
<b>7</b>	160	42	160	210 230 <sup>f</sup> 280	4.17 4.18 4.09	9.43 (d, <i>J</i> = 2.52, 1H); 8.73 (dd, <i>J</i> = 6.53 and 1.68, 1H); 8.45 (dd, <i>J</i> = 8.05 and 1.68, 1H); 6.66–7.51 (m, 4H); 3.74 (s, 2H)	3370, 3190, 3040, 1615, 1545, 1185, 1015

<sup>a</sup> Spectral data of all the compounds were obtained in this research.

<sup>b</sup> Crystallization solvent: diethyl ether/petroleum ether.

<sup>c</sup> Given in literature as 109–110°C (Ciba, 1962a,b).

<sup>d</sup> Given in literature as 153–154°C (Ciba, 1962a,b).

<sup>e</sup> Given in literature as 102–103°C (Ciba, 1962a,b).

<sup>f</sup> Given as shoulder.

and antimycotic assays (Charles et al., 1979; Yalçın et al., 1992). Further dilutions of the compounds and reference drugs in the test medium were furnished at the required quantities of 100, 50, 25, 12.5, 6.25, 3.12, 1.56 and 0.78 µg/ml concentrations. The minimum inhibitory concentrations (MIC) were determined using the method of two-fold serial dilution (Shadomy and Espinel, 1980; Yalçın et al., 1990, 1992; Yalçın and Şener, 1993). 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 to be inactive in culture medium.

The antimicrobial activity of the compounds was examined with respect to their in vitro growth inhibitory activity against some Gram-negative and Gram-positive bacteria and a yeast *C. albicans* RSKK 628. The origins of the bacterial strains were *S. aureus* ATCC 6538, *Streptococcus faecalis* ATCC 10541 as Gram-positive and *E. coli* ATCC 10536, *K. pneumoniae* NTCC 52211,

and *Ps. aeruginosa* RSKK 355 as Gram-negative bacteria.

Ampicillin (13), amoxicillin (14), erythromycin (15), chloramphenicol (16), haloprogin (17), and clotrimazole (18) were used as reference drugs. The observed data on the antimicrobial activity of the compounds and the reference drugs are listed in Table 2.

For the antibacterial assay, the cultures were prepared in Mueller-Hinton broth (Difco) for all the bacteria after 24 h of incubation at  $37 \pm 1^\circ\text{C}$ . 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  $37 \pm 1^\circ\text{C}$ , the last tube with no growth of microorganisms was recorded to represent the MIC expressed in µg/ml.

For the antimycotic assay, the yeast *C. albicans* was maintained in Sabouraud dextrose broth (Difco) after incubation for 24 h at  $25 \pm 1^\circ\text{C}$ . Testing was performed in Sabouraud dextrose broth at pH 7.4, the two-fold serial dilution tech-

Table 2

In vitro antimicrobial activity of compounds 1–10 and the reference drugs 13–18 (MIC in µg/ml)

Compound	Microorganisms					
	Gram-positive		Gram-negative			Fungus
	<i>Sa</i>	<i>Sf</i>	<i>Ec</i>	<i>Kp</i>	<i>Pa</i>	<i>Ca</i>
1	> 100	> 100	> 100	100	> 100	> 100
2	> 100	> 100	> 100	100	> 100	> 100
3	25	25	25	12.5	25	12.5
4	25	25	12.5	12.5	25	25
5	25	25	25	25	25	25
6	25	25	12.5	12.5	25	25
7	25	25	25	12.5	25	12.5
8	12.5	25	25	12.5	12.5	25
9	12.5	100	12.5	12.5	12.5	12.5
10	25	25	25	6.2	12.5	12.5
13 ampicillin	0.3	0.3	1.5	12.5	> 200	–
14 amoxicillin	0.3	0.3	1.5	12.5	> 200	–
15 erythromycin	25	1.5	50	50	25	–
16 chloramphenicol	12.5	6.2	25	12.5	25	–
17 haloprogin	–	–	–	–	–	3.1
18 clotrimazole	–	–	–	–	–	6.2

<sup>a</sup> *Sa*, *Staphylococcus aureus*; *Sf*, *Streptococcus faecalis*; *Ec*, *Escherichia coli*; *Kp*, *Klebsiella pneumoniae*; *Pa*, *Pseudomonas aeruginosa*; *Ca*, *Candida albicans*.

nique being performed. A set of tubes containing only inoculated broth was kept as controls. After incubation for 48 h at  $25 \pm 1^\circ\text{C}$ , the last tube with no growth of yeast was recorded to represent the MIC expressed in  $\mu\text{g/ml}$ .

### 2.3. Quantum-chemical calculations

Quantum-chemical calculations were run on an IBM 360/158 computer using Lowe's program (1978) which was based on Hückel molecular orbital (HMO) considerations. Coplanar forms of the molecules were assumed in HMO type calculations within the zero differential overlap (ZDO) approximation (Heilbronner and Bock, 1976). Heteroatom parameters were taken from the literature (Streitwieser, 1961). Oxygen and nitrogen atoms embedded in the five-membered ring of the benzoxazole structure were thought to be the effective part of these heterocyclic compounds.

Table 3 indicates the highest occupied molecular orbital ( $\epsilon_{\text{HOMO}}$ ) and lowest unoccupied molecular orbital ( $\epsilon_{\text{LUMO}}$ ) energy levels (in  $\beta$  units) of compounds **1–10** and the respective molecular orbital coefficients of oxygen and nitrogen atoms ( $C_{\text{HOMO(O)}}$ ,  $C_{\text{LUMO(O)}}$  and  $C_{\text{HOMO(N)}}$ ,  $C_{\text{LUMO(N)}}$ ) in the oxazolo moiety of certain benzoxazole derivatives used in the present study. The electrophilic ( $S^E$ ) and nucleophilic ( $S^N$ ) superdelocal-

izabilities (Franke, 1984) of oxygen and nitrogen atoms in the oxazolo moiety of the benzoxazole structures given in Table 3 were calculated by using Eq. 1 and 2 (Streitwieser, 1961; Heilbronner and Bock, 1976):

$$S_r^N = 2 \sum_j^{\text{unocc.}} C_{jr}^2 / -\epsilon_j \quad (1)$$

$$S_r^E = 2 \sum_j^{\text{occ.}} C_{jr}^2 / \epsilon_j \quad (2)$$

where  $\epsilon_j$  denotes the molecular orbital energy in  $\beta$  units.  $C_{jr}$  represents the molecular orbital coefficient of atom  $r$  in the  $j$ -th molecular orbital.

### 3. Results and discussion

In order to establish the structure activity relationships, compounds **1–10** were screened against two Gram-positive, three Gram-negative bacteria and the yeast *C. albicans* by using the two-fold serial dilution technique. Data for the antimicrobial activity of the compounds are given in Table 2 with a comparison of some of the tested reference drugs (compounds **13–18**).

The microbiological data given in Table 2 show that among the screened microorganisms, 5-substituted 2-(3-pyridyl)benzoxazoles exhibited a sig-

Table 3

Values from quantum-chemical calculation of the substituted benzoxazoles **1–10**

Compound	$\epsilon_{\text{HOMO}}$	$\epsilon_{\text{LUMO}}$	$C_{\text{HOMO(O)}}^a$	$C_{\text{LUMO(O)}}^a$	$C_{\text{HOMO(N)}}^b$	$C_{\text{LUMO(N)}}^b$	$S_{\text{O}}^E^c$	$S_{\text{O}}^N^c$	$S_{\text{N}}^E^d$	$S_{\text{N}}^N^d$
<b>1</b>	0.622	-0.483	0.031	-0.195	-0.426	-0.376	0.892	0.235	1.140	0.867
<b>2</b>	0.635	-0.470	0.041	0.190	-0.432	0.369	0.891	0.235	1.139	0.865
<b>3</b>	0.603	-0.533	0.021	-0.193	-0.442	-0.358	0.894	0.218	1.201	0.768
<b>4</b>	0.601	-0.533	0.015	-0.194	-0.437	-0.358	0.896	0.218	1.201	0.768
<b>5</b>	0.599	-0.424	0.008	0.023	-0.043	-0.073	0.897	0.222	1.202	0.770
<b>6</b>	0.594	-0.533	-0.014	-0.196	-0.409	-0.356	0.909	0.215	1.204	0.759
<b>7</b>	0.587	-0.533	-0.040	-0.195	-0.370	-0.356	0.908	0.216	1.205	0.762
<b>8</b>	0.600	-0.539	0.019	0.196	-0.441	0.362	0.884	0.218	1.201	0.769
<b>9</b>	0.597	-0.424	0.006	0.024	-0.429	-0.072	0.897	0.222	1.203	0.770
<b>10</b>	0.584	-0.539	-0.040	0.199	-0.371	0.361	0.908	0.216	1.205	0.763

<sup>a</sup> Molecular orbital coefficients of the oxygen atom in the oxazolo moiety of the benzoxazole derivatives.

<sup>b</sup> Molecular orbital coefficients of the nitrogen atom in the oxazolo moiety of the benzoxazole derivatives.

<sup>c</sup> Electrophilic ( $S_{\text{O}}^E$ ) and nucleophilic ( $S_{\text{O}}^N$ ) superdelocalizability values of the oxygen atom in the oxazolo moiety of the benzoxazole derivatives.

<sup>d</sup> Electrophilic ( $S_{\text{N}}^E$ ) and nucleophilic ( $S_{\text{N}}^N$ ) superdelocalizability values of the nitrogen atom in the oxazolo moiety of the benzoxazole derivatives.

nificant antimicrobial activity in *E. coli* (compounds **4** and **6**), *K. pneumoniae* (compounds **3**, **4**, **6** and **7**) which are Gram-negative rods and the yeast *C. albicans* (compounds **3** and **7**) at a concentration of 12.5 µg/ml.

When the potencies of compounds **3–7** were compared to those of the tested reference drugs, they showed a better in vitro antibacterial activity than erythromycin in *E. coli* and *K. pneumoniae*. Moreover, compounds **3**, **4**, **6** and **7** were found to be as active as the other reference drugs against *K. pneumoniae*. Additionally, compounds **3–7** also expressed preferred activities against *Ps. aeruginosa* rather than the reference drugs **13** and **14**, having the same MIC values as **15** and **16**.

Despite the insignificant activity of 2-(2-pyridyl)- and 2-(4-pyridyl)benzoxazoles (**1** and **2**) against the screened microorganisms at MIC values over 100 µg/ml, the 2-(3-pyridyl)benzoxazole derivatives (**3–7**) inhibited the growth of microorganisms, having MIC values between 25 and 12.5 µg/ml as shown in Table 2. This improvement in activity for compounds **3–7** could be defined by the nitrogen atom being at different positions in the pyridyl moiety attached to the second position of the benzoxazole ring.

Table 3 indicates that the  $\epsilon_{\text{HOMO}}$  energy levels of compounds **1** and **2** are lowered in comparison with their analogs **3** and **8**. On the other hand, the  $\epsilon_{\text{LUMO}}$  energy levels of the above-mentioned compounds follow the order of the 2-phenyl > 2-(3-pyridyl) > 2-(2-pyridyl) > 2-(4-pyridyl)benzoxazole structures, respectively.

Although the nucleophilic superdelocalizability values of oxygen or nitrogen atoms ( $S_{\text{O}}^{\text{N}}$ ,  $S_{\text{N}}^{\text{N}}$ ) in the oxazolo moiety for 2-phenyl- and 2-(3-pyridyl)benzoxazoles are pairwise comparable with each other, as are those of the 2-(2-pyridyl)- and 2-(4-pyridyl)-substituted analogs, the main type of interaction at the binding site should be via donation of the lone pairs of oxygen or nitrogen atoms in the oxazolo moiety of the benzoxazole ring to any electrophilic site(s). Hence, more emphasis should be given to the  $S_{\text{O}}^{\text{E}}$  and  $S_{\text{N}}^{\text{E}}$  values.

Examination of the electrophilic superdelocalizability values of the oxygen and nitrogen atoms ( $S_{\text{O}}^{\text{E}}$ ,  $S_{\text{N}}^{\text{E}}$ ) in the oxazolo moiety of the heterocyclic

system reveals that the  $S_{\text{N}}^{\text{E}}$  values of the nitrogen atom are also pairwise comparable for 2-phenyl- and 2-(3-pyridyl)benzoxazoles. This observation is in agreement with the microbiological results, whereas the  $S_{\text{O}}^{\text{E}}$  values given in Table 3 for oxygen atom are contradictory to the microbiological data. All these results imply that the nitrogen atom lone pair electrons in the oxazolo moiety of the benzoxazole system should contribute to any electrophilic region rather than oxygen electrons at the binding site.

As shown in Table 3, substitutions at position 5 on the benzoxazole ring generally do not affect  $S_{\text{N}}^{\text{E}}$  and  $S_{\text{N}}^{\text{N}}$  values considering at the nitrogen atom in the oxazolo moiety. Thus, the theoretical expectation is that the primary effect of 5-substituents on the effective site should not be electronic in nature. This expectation is generally fulfilled by the MIC values given in Table 2. In the light of theoretical considerations, all these observations imply that the substituent at position 5 on benzoxazoles, irrespective of its kind (electron donor or acceptor), exerts some influence on the activity constructively or destructively depending on the type of the screened microorganism. For instance, 5-nitro-2-phenylbenzoxazole (compound **9**) is as effective as 2-phenylbenzoxazole (compound **8**) against *S. aureus*. However, it is less effective against *St. fecalis* and more effective against *E. coli* as compared to each other.

#### 4. Conclusion

The results shown in Table 2 reveal that when the antimicrobial effects of 2-(2-pyridyl)-, 2-(3-pyridyl)- and 2-(4-pyridyl)benzoxazole derivatives are compared, compounds **3–7** are more significantly active than compounds **1** and **2**. The activity contribution results also indicate that 2-phenyl- and 2-(3-pyridyl)benzoxazoles exhibit bio-isosteric effects for antimicrobial activity. On the other hand, substitution of position 5 of the fused heterocyclic nucleus causes changes in the intensity of the activity due to the type of the microorganism screened.

Additionally, the observed theoretical quantum-chemical calculations given in Table 3 for the structure-activity relationships show that the electrophilic superdelocalizability of the nitrogen atom ( $S_N^E$ ) in the oxazolo moiety of the benzoxazole ring is related to the activity.

### Acknowledgment

We would like to thank the Research Fund of Ankara University (Grant No. 88 30 00 08) for financial support of this research.

### References

- Charles, E.S., Agrawal, V.K., Sharma, S., Iyer, R.N. and Srivastava, O.P., Synthesis of 2,5-disubstituted benzimidazoles as potent antihookworm and antimicrobial agents. *Eur. J. Med. Chem. Chim. Ther.*, 14 (1979) 435–438.
- Ciba Ltd., *Br. Patent Office* 895,431 (1962a).
- Ciba Ltd., *Br. Patent Office* 901,648 (1962b).
- Franke, R., Electronic effects: Application of quantum chemical parameters. In Nauta, W.T. and Rekker, R.F. (Eds), *Theoretical Drug Design*, Elsevier, Amsterdam, 1984, pp. 115–123.
- Heilbronner, E. and Bock, H., *The HMO-Model and its Applications*, Wiley, New York, 1976, p. 93.
- Hisano, T., Ichikawa, M., Tsumoto, K. and Tasaki, M., Synthesis of benzoxazoles, benzothiazoles and benzimidazoles and evaluation of their antifungal, insecticidal and herbicidal activities. *Chem. Pharm. Bull.*, 30 (1982) 2996–3004.
- Lowe, J.P., *Quantum Chemistry*, Academic Press, New York, 1978, pp. 538–542.
- Şener, E., Yalçın, İ. and Sungur, E., QSAR of some antifungal benzoxazoles and oxazolo(4,5-*b*)pyridines against *C. albicans*. *Quant. Struct.-Act. Relat.*, 10 (1991) 223–228.
- Shadomy, S. and Espinel, A., *Manuel of Clinical Microbiology*, Am. Soc. Microbiol., Washington, DC, 1980, p. 647.
- Streitwieser, A., Jr., *Molecular Orbital Theory for Organic Chemists*, Wiley, New York, 1961, pp. 33–134.
- Yalçın, İ. and Şener, E., QSARs of some novel antibacterial benzimidazoles, benzoxazoles and oxazolopyridines against an enteric gram-negative rod; *K. pneumoniae*. *Int. J. Pharm.*, 98 (1993) 1–8.
- Yalçın, İ., Ören, İ., Şener, E., Akın, A. and Uçartürk, N., The synthesis and the structure-activity relationships of some substituted benzoxazoles, oxazolo(4,5-*b*)pyridines, benzothiazoles and benzimidazoles as antimicrobial agents. *Eur. J. Med. Chem.*, 27 (1992) 401–406.
- Yalçın, İ., Şener, E., Özden, T., Özden, S. and Akın, A., Synthesis and microbiological activity of 5-methyl-2-(*p*-substituted phenyl)benzoxazoles. *Eur. J. Med. Chem.*, 25 (1990) 705–708.