The synthesis and the structure–activity relationships of some substituted benzoxazoles, oxazolo(4,5-b)pyridines, benzothiazoles and benzimidazoles as antimicrobial agents

I Yalçın¹, İ Ören¹, E Şener¹, A Akın², N Uçartürk²

¹Ankara University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry; ²Ankara University, Faculty of Pharmacy, Department of Microbiology, 06100 Tandogan, Ankara, Turkey

(Received 11 April 1991; accepted 26 November 1991)

Summary — The synthesis of a new series of 2,5-disubstituted benzoxazoles 4a–f, 2-substituted oxazolo(4,5-*b*)pyridines 5a, b, benzothiazoles 6a, b and benzimidazoles 7a, b is 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, and a fungus *Candida albicans*. 4b, 4e and 4f were found to be more active than the others against *Klebsiella pneumoniae* at a MIC value of 12.5 μ g/ml. All the derivatives 4–7 exhibited significant antimycotic activity against *C albicans*. The antibacterial and antimycotic activities of 4–7 are also compared with several standard drugs.

benzoxazoles / oxazolo(4,5-b)pyridines / benzothiazoles / benzimidazoles / antibacterial activity / antimycotic activity / SAR

Introduction

The development of new and different antimicrobial agents has been a very important step and much of the research program efforts are directed toward to the design of new and available drugs, because of the unsatisfactory status of present treatments of microorganisms, drug side effects, and the acquisition by the infecting organisms of resistance to the present drugs [1].

A review of the literature revealed that many effective antimicrobial agents have a heterocyclic system in their molecule [2, 3]. Since thiabendazole has been found to be effective in the treatment of helmintic diseases with good clinical efficacy in topical therapy of dermatophytic infections [4, 5], several substituted benzimidazole derivatives have been reported for their antimicrobial activity in previous years [6]. Recent observations suggest that apart from the substituted benzimidazole derivatives, several analogs of this ring system, such as benzoxazole and benzothiazole derivatives also indicate potential activity with lower toxicity in the antimicrobial therapeutic approach in man [7-11]. Furthermore, studies on these structures showed that substitution on position 2 was prominently studied revealing that this position is decisive for the activity, whereas position 5 determines the intensity of the activity [12–14]. Consequently, there is a great interest in investigating the role of the mentioned heterocyclic nuclei in order to ascertain if they would offer and advantage over the known clinically used antimicrobial drugs [15].

Considering these phenomena, in the last few years, we synthesized different derivatives of 5-substituted-2-(p-substitutedphenyl)benzoxazoles 1 [16, 17], 5-substituted-2-(p-substitutedbenzyl)benzoxazoles 2 [18], and 2-(p-substitutedphenyl)oxazolo(4,5-b)pyridines 3 [19] and observed *in vitro* antimicrobial activity of compounds 1 against some Gram-positive, Gram-negative bacteria and the fungus *C albicans* in our laboratories [17].



- 1 Z=CH Y= R=H, Cl, NO₂, NH₂, CH₃ R₁ = H, CH₃, C₂H₅, F, Br, Cl, NHCH₃, NO₂, NH₂, C(CH₃)₃, NHCOCH₃, NH(CH₃)₂, OCH₃
- 2 Z=CH Y=CH₂ R=H, Cl, NO₂ $R_1 = H$, OCH₃, Cl, Br, NO₂
- **3** Z=N Y= R=H R₁ = Cl, Br, NO₂, NH₂, OC₂H₅, OCH₃, CH₃, C₂H₅, C(CH₃)₃

In this study, a new series of compounds 4–7, including four isosteric heterocyclic nuclei have been selected as the target structures for the comparison of their antimicrobial effects. They were synthesized and their *in vitro* antibacterial and antimycotic activities are described. Additionally, the antimicrobial activity of the previously synthesized compounds 2a–p and 3a–i are also determined by testing them with the microorganisms used in the present study.

Chemistry

The synthesis of the compounds 2,5-disubstituted benzoxazoles 4, 2-substituted oxazolo(4,5-b) pyridines 5, benzothiazoles 6, and benzimidazoles 7 were performed through heating carboxylic acids with appropriate *o*-substituted anilines by means of several dehydrating agents in a one-step procedure.



Polyphosphoric acid (PPA) or polyphosphate ester (PPE), which contains anhydride groups to combine with water molecules formed during the reaction period in order to prevent the solvolyzation of oxazolo and thiazolo rings under hot aqueous acidic conditions, was used in the synthesis of compounds 4, 5 and 6 [17, 20, 21]. PPE has been found to be more suitable and easier to handle as a cyclodehydration reagent than PPA for the synthesis of 2-substituted benzothiazoles 6, even under mild conditions.

During the synthesis of 7, aqueous hydrochloric acid was used as the condensation reagent, according to the well-known Phillips' method [22]. However, this route was successful neither for preparation of benz-oxazoles nor oxazolo(4,5-b)pyridines and benzothiazoles.

Compounds 4–7 were prepared as new products except 6a [23] and 7a [24]. The structures of all the derivatives 4a–f, 5a, b, 6a, b and 7a, b were supported by elemental analysis and spectral data. The UV, IR and ¹H NMR spectra are in agreement with the proposed structures. Physical and spectral data of the compounds are reported in table I.

Results

In vitro antibacterial activity

For the antibacterial activity of 4–7, 3 Gram-positive and 3 Gram-negative bacteria strains were screened using two-fold serial dilution technique. The results reported in table II indicate that compounds 4–7 are able to inhibit *in vitro* growth of a number of bacteria having MIC values between 50 and 12.5 μ g/ml. Microbiological data showed that among the screened bacteria, 4–7 exhibited a preferable antibacterial activity in *B subtilis* which is an aerobic spore-forming Gram-positive rod and some enteric Gram-negative non-spore-forming rods such as *K pneumoniae* and *P aeruginosa*. In particular, 4b, 4e and 4f were found to be more active in *K pneumoniae* than the other compounds at a concentration of 12.5 μ g/ml.

When compounds 4-7 were compared to the tested standard drugs, they showed a better *in vitro* antibacterial activity in *P aeruginosa*, apart from gentamycin.

In vitro antimycotic activity

For the observation of the *in vitro* antimycotic activity, the compounds were tested against *C albicans*. All compounds **4–7** were found significantly active against *C albicans* as MIC values of 12.5 μ g/ml and the antimycotic potency of these compounds was close to the activity of the tested clinically used drugs **20** and **21**.

Discussion

The results shown in table II reveal that the four different heterocyclic nuclei at compounds 4–7 indicate bioisosteric effects in the antimicrobial activity for the screened microorganisms. Substitution of position 2 on the heterocyclic ring with 2-phenylethyl or 2-cyclohexylethyl groups produces no difference in the determination of the activity. On the other hand, substitution of position 5 with a nitro and/or amino group causes an increase in the intensity of the antibacterial activity for *K pneumoniae* but this advantage cannot be achieved with the chlorine atom. However, these results point out that the heterocyclic fused ring systems at these compounds are necessary for the antimicrobial (primarily antimycotic) activity.

Most of the compounds already described in table II are the higher homologous types of the previously synthesized compounds 2 and 3. In order to establish structure activity relationships in this group of compounds, *in vitro* antimicrobial activity of the compounds 2a-p and 3a-i was also determined and has been shown in table III. Table I. Physical properties, preparation and spectral data of the compounds 4-7.



. X Methoc	X Method	fethoc	~	Reaction temp('C)	Reaction time(h)	Yield (x)	(<i>з.</i>) д ^д й	رال M. 10.1 (1)	V log E	NMR & ppm (J in Hz)	IR cm ⁻¹
H phenyl A	henyl A		1	120	3	58	53	217 235 280	4.14 4.10 3.86	3.22 (s,4H); 7.22 (s,5H); 7.25 (d,J=6.5,1H); 7.32 (dd,J=6.5 and 1.8,1H); 7.64 (d,J=1.8,1H)	3095, 2940, 1610, 1570 1455, 1260
H phenyl A	henyl A	A		130	5	41	75	227 278	4.35 3.84	3.28 (s,4H); 7.27 (s,5H); 7.55 (d,J=8.9,1H); 8.27 (dd,J=8.9 and 2.4,1H); 8.55 (d,J=2.4,1H)	3100, 2920, 1620, 1575 1525, 1450, 1350, 1260
H cyclohexyl A	yclohexyl A	A 1		180	~	64	150 ^c	209 232	3.90 3.92	0.64 - 2.04 (m,13H); 2.88 (t,J=8.5,2H); 7.80- 7.30 (m,2H); 7.35-7.82 (m,2H)	3030, 2980, 1635, 1590 1470, 1260
H cyclohexyl A	:yclohexyl A	A I		130	3.5	60	36	214 235 280	4.06 4.05 3.83	0.69-2.03 (m.13H); 2.92 (t.J=6.6.2H); 7.24- 7.38 (m,2H); 7.63 (d,J=1.7,1H)	3100, 2930, 1610, 1570 1455, 1260
H cyclohexyl A	syclohexyl A	ΓV		140	0	46	51	232 277	4.25 3.88	0.71-2.0 (m.13H); 3.08 (t, J=8.3,2H); 7.53 (d, J=10.3,1H); 8.28 (dd, J=10.3 and 2.8,1H); 8.59 (d, J=2.8,1H)	3120, 2985, 1649, 1580 1550, 1450, 1365, 1270
H cyclohexyl A	syclohexyl A	T A		180	8	59	64	220 305	5.14 4.50	0.60-2.04 (m.13H); 2.88 (t.J=8.5,2H); 3.65 (s,2H); 6.66 (dd,J=8.4 and 2.3,1H); 6.93 (d, J=2.3,1H); 7.22 (d,J=8.4,1H)	3410, 3230, 3030, 2920 1640, 1570, 1450, 1270
i phenyl A	phenyl A	A		120	8	35	52	211 277	3.85 3.83	3.28 (s,4H); 7.27-7.38 (m,6H); 7.82 (dd,J= 6.8 and 1.4,1H); 8.58 (dd,J=6.4 and 1.4,1H)	3100, 2960, 1635, 1540 1425, 1270
v cyclohexyl A	cyclohexyl A	l A		130	2	64	61	224 277	3.86 4.12	0.67-2.04 (m.13H); 3.01 (t, J=8.2H); 7.29 (dd, J=6.8 and 6.4,1H); 7.79 (dd, J=6.8 and 1.4,1H); 8.55 (dd, J=6.4 and 1.4,1H)	3020, 2990, 1625, 1575 1470, 1275
CH phenyl E	phenyl F	щ	~	70	1.5	76	60	220 254	4.21 3.92	3.25 (s,4H); 7.22 (s,5H); 7.32-7.60 (m,2H); 7.70 - 8.12 (m,2H)	3105, 2920, 1610, 1530 1450, 1310
CH cyclohexyl E	cyclohexyl E	ц.	~	80	1.5	62	204 ^c	250 283	3.50 3.24	0.60-2.10 (m,13H); 3.20 (t, <i>J</i> =8,2H); 7.04- 7.58 (m,2H); 7.65-8.12 (m,2H)	3100, 2930, 1610, 1540 1455, 1310
CH phenyl (phenyl (0	~	100	ີ	56	187	212 244 274	4.27 3.82 3.88	3.20 (s,4H); 7.05-7.35 (m,7H); 7.40-7.62 (m,2H)	3230, 3090, 2900, 1630 1550, 1450, 1280
CH cyclohexyl C	cyclohexyl C	c T		100	ব	49	185	209 243 274	4.20 3.77 3.82	0.62-1.93 (m,13H); 2.95 (t,J=8,2H); 7.10- 7.35 (m,2H); 7.40-7.72 (m,2H)	3240, 3080, 2985, 1640 1540, 1460, 1280

^aThe spectral data of all the compounds have been obtained in this research; ^bCrystallization solvent; diethyl ether/petroleum ether for **4a**, **b**, **d**, **e**, **f**, **5a**, **b**, **6a** and benzene/petroleum ether for **7a**, **b**. ^cGiven as boiling points.

Comp			Mi	croorganisms	1		
	G	Fram-positive		G	ram-negative		Fungus
	Sa	Ŝf	Bs	Ec	Kp	Pa	Ca
4 a	50	50	25	50	25	25	12.5
4b	50	50	25	50	12.5	25	12.5
4 c	50	50	25	50	25	25	12.5
4 d	50	50	25	50	25	25	12.5
4e	50	50	25	50	12.5	25	12.5
4f	50	50	25	50	12.5	25	12.5
5a	50	50	25	50	25	25	12.5
5b	50	50	25	50	25	25	12.5
6a	50	50	25	50	25	25	12.5
6b	50	50	25	50	25	25	12.5
7a	50	50	25	50	25	25	12.5
7b	50	50	25	50	25	25	12.5
15 Ampicillin	0.78	0.78	0.78	3.12	12.5	> 200	-
16 Amoxycillin	0.78	0.78	0.78	3.12	12.5	> 200	_
17 Tetracycline	0.78	0.78	0.78	3.12	3.12	50	_
18 Gentamycin	< 0.78	12.5	0.78	3.12	1.56	12.5	_
19 Streptomycin	3.12	100	50	1.56	1.56	100	_
20 Oxiconazole	_	_	_	_	_	_	6.25
21 Haloprogin	-	_		-	-	-	6.25

Table II. The *in vitro* antimicrobial activity of the compounds 4–7 and the standard drugs 15–21 (MIC in μ g/ml).

^aAbbreviations; Sa, Staphylococcus aureus; Sf, Streptococcus faecalis; Bs, Bacillus subtilis; Ec, Escherichia coli; Kp, Klebsiella pneumoniae; Pa, Pseudomonas aeruginosa; Ca, Candida albicans.

When the results shown in table II and III are compared, the following conclusions for the SAR can be drawn:

separation of the benzoxazole ring system from a phenyl moiety at position 2 by an ethylene or a methylene group as a linking element does not produce any difference in the antibacterial activity; substitution of position R on the heterocyclic nucleus is found to be more important than R_1 in improving the activity; 2-phenyloxazolo(4,5-*b*)pyridine ring system (see compounds **3a–i** in table III) appears as the favorable structure in the determination of the antibacterial activity in some bacteria.

Experimental protocols

Chemistry

Kieselgel HF₂₅₄ chromatoplates (0.3 mm) were used for TLC and the solvent systems were chloroform:toluene (30:5) for compounds **4a**, **b**, **d**, **e**, **5a**, chloroform:diethyl ether (10:1) for **4f**, chloroform:methanol (30:5) for **5b**, chloroform:acetone (10:2) for **7a**, **b**, and only chloroform for **4c**, **6a**, **b**. All melting and boiling points were taken on a Buchi SMP 20 capillary apparatus and uncorrected. IR spectra were recorded by Pye Unicam SP-1025 with KBr discs except **4c** and **6b** which were taken in nujol. ¹H NMR spectra were obtained with a Bruker 80 MHz spectrometer in d₆-chloroform and TMS was used as an internal standard. UV maxima were measured on a Pye Unicam SP-1700 spectrophotometer in methanol at 10^{-4} M concentration. Elemental analyses were carried out with a Perkin Elmer model 240-C apparatus. The results of the elemental analyses (C, H, N) were within $\pm 0.4\%$ of the calculated amounts.

The compounds were prepared by three general methods which differed according to the dehydrating agent used. The cyclodehydration reagent PPE was prepared in our laboratory by the method described in [21]. 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 PEE as a viscous, colorless to yellowish substance which forms a stiff gel below 0°C.

Method A (compounds 4a-f and 5a, b)

A mixture of 2-hydroxy-5-substitute aniline 8 or 2-amino-3hydroxypyridine 9 (0.01 mol) and 3-phenylpropionic acid 12 or 3-cyclohexylpropionic acid 13 (0.015 mol) was heated over 100°C in PPA (12 g). At the end of the reaction period, the residue was poured into ice-water and neutralized with excess of 10% NaOH solution. The precipitate was collected, washed, Table III. The antimicrobial activity of the previously synthesized compounds 2a-p and 3a-i (MIC in µg/ml).

Comp	R	R_{I}	Ζ	Y	Sa	Sf	Bs	Ec	Кр	Pa	Ca
2a	н	Н	CH	CH ₂	50	50	50	50	25	50	25
2b	Н	OCH ₃	CH	CH_{2}	50	50	50	50	25	50	25
2c	Н	Br	CH	CH_{2}	50	50	50	50	25	50	25
2d	Н	Cl	CH	CH_2^{-}	50	50	50	50	25	50	25
2e	Н	NO_2	CH	CH_{2}	50	50	50	50	25	50	25
2f	Cl	НĨ	CH	CH_{2}	50	50	25	50	25	25	25
2g	Cl	OCH ₃	CH	CH ₂	50	50	25	50	25	25	25
2h	Cl	Br	CH	CH_{2}	50	50	25	50	25	25	25
2i	Cl	NO_2	CH	CH_2	50	50	25	50	25	25	25
2k	Cl	Cl	CH	CH_2	50	50	25	50	25	25	25
21	NO_2	Н	CH	CH_2	50	50	25	50	12.5	25	12.5
2m	NO_2^{-}	OCH ₃	CH	CH_2^-	50	50	25	50	12.5	25	12.5
2n	NO_2	Br	СН	CH_2	50	50	25	50	12.5	25	12.5
20	NO_2	Cl	CH	CH_2	50	50	25	50	12.5	25	12.5
2р	NO_2	NO_2	CH	CH_2	50	50	25	50	12.5	25	12.5
3a	Н	CH_3	Ν	_	25	25	25	25	12.5	25	12.5
3b	Н	C_2H_5	Ν	_	25	25	25	25	12.5	25	12.5
3c	Н	OCH ₃	Ν	_	25	25	25	25	12.5	25	12.5
3d	Н	OC_2H_5	Ν	_	25	25	25	25	12.5	25	12.5
3e	Н	NH_2	Ν	_	25	25	25	25	12.5	25	12.5
3f	Н	NO_2	Ν	-	25	25	25	25	12.5	25	12.5
3g	Н	$C(CH_3)_3$	Ν	_	25	25	25	25	12.5	25	12.5
3h	Н	C1	Ν		25	25	25	25	12.5	25	12.5
3i	Н	Br	Ν	_	25	25	25	25	12.5	25	12.5

dried and extracted with benzene to separate from impurities. After the evaporation of the solvent *in vacuo*, the crude product was obtained and crystallized. Due to lack of precipitation, the isolation of compound **4c** was pursued by direct extraction of the aqueous alkaline solution with benzene. After combining the benzene extracts, it was dried over anhydrous sodium sulfate, the solvent was evaporated *in vacuo* and the residue was obtained to give **4c** as a viscous, yellowish substance.

Method B (compounds 6a, b)

A mixture of o-aminothiophenol 10 (0.01 mol) and 12 or 13 (0.015 mol) was heated at bath-temperature in PPE (10 g). At the end of the reaction period, the mixture was poured into icewater and neutralized with an excess of NaHCO₃. After being extracted with benzene, the combined benzene extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was obtained to give **6a** and crystallized. **6b** was obtained as a viscous, yellowish substance.

Method C (compounds 7a, b)

A mixture of o-phenylenediamine 11 (0.01 mol), 12 or 13 (0.015 mol) and 6 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 NaHCO₃. 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 crystallized.

Microbiology

For both the antibacterial and the antimycotic assays, the compounds were dissolved in absolute ethanol (0.8 mg/ml) [25]. 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 [17, 25, 26]. 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* RSKK 250, *Streptococcus faecalis* RSKK 500, *Bacillus subtilis* ATCC 6033 as Gram-positive and *Escherichia coli* RSKK 313, *Klebsiella pneumoniae* RSKK 256, and *Pseudomonas aeruginosa* RSKK 356 as Gramnegative 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 15, amoxycillin 16, tetracycline 17, gentamycin 18, streptomycin 19, oxiconazole 20, and haloprogin 21 were



used as standard drugs. The observed data on the antimicrobial activity of the compounds and the standard drugs are given in tables II and III.

Antibacterial assay

The cultures were obtained in Mueller-Hinton broth (Difco) for all the bacteria after 24 h of incubation at $37 \pm 1^{\circ}$ C. Testing was carried out in Mueller-Hinton broth at pH 7.4 and the twofold serial dilution technique was applied. A set of tubes containing only inoculated broth was kept as controls. After incubation for 24 h at $37 \pm 1^{\circ}$ C, the last tube with no growth of microorganism was recorded to represent MIC expressed in μ g/ml.

Antimycotic assay

The yeast *C* albicans was maintained in Sabouraud dextrose broth (Difco) after incubation for 24 h at $25 \pm 1^{\circ}$ C. Testing was performed in Sabouraud dextrose broth at pH 7.4 and the twofold serial dilution technique was applied. A set of tubes containing only inoculated broth was kept as controls. After incubation for 48 h at $25 \pm 1^{\circ}$ C, the last tube with no growth of yeast was recorded to represent MIC expressed in µg/ml.

Acknowledgment

The authors wish to thank the Research Fund of Ankara University for financial support.

References

- 1 Javetz E, Melnick JL, Adelberg EA (1984) In: Review of Medical Microbiology. Lange, California, 122
- 2 Daidone G, Maggio B, Schillaci D (1990) Pharmazie 45, 441-442
- 3 Martin AR (1982) In: Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry (Doerge RF, ed) JB Lippincott, Philadelphia, 129–188
- 4 Brown HD, Matzuk AR, Ilves IR, Peterson LH, Harris SA, Sarett LH, Egerton JR, Yakstis JJ, Campbell WC, Cuckler AC (1961) J Am Chem Soc 83, 1764–1765
- 5 McFarland JW (1972) Fortschr Arzneimittelforsch 16, 157–193

- 6 Islip PJ (1980) In: Burger's Medicinal Chemistry Part II (Wolff ME, ed) John Wiley & Sons, New York, 481– 530
- 7 Geigy Chemical Corporation (1971) US Patent Office 3, 586, 670
- 8 Brown DJ, Dunlap WC, Grigg GW, Danckwerts L (1978) Aust J Chem 31, 447–450
- 9 Philips MK, Kell DB (1981) FEMS Microbiology Letters 11, 111–113
- 10 Haugwitz RD, Angel RG, Jacobs GA, Maurer BV, Narayanan VL, Cruthers LR, Szanto J (1982) J Med Chem 25, 969–974
- 11 Hisano T, Ichikawa M, Tsumoto K, Tasaki M (1982) Chem Pharm Bull 30, 2996-3004
- 12 Pedini M, De Meo G, Ricci A, Bastianini L, Jacquignon P (1990) Il Farmaco, Ed Sci 45, 303–312
- 13 Evans D, Dunwell DW, Hicks TA (1975) J Med Chem 18, 1158–1159
- 14 Holder GM, Little PJ, Ryan AJ, Watson TR (1976) Biochem Pharmacol 25, 2747–2750
- 15 Rubino S, Unger E, Fogu G, Cappuccinelli P (1982) Zeitschrift Allg Mikr 22, 127–131
- 16 Şener E, Yalçın İ, Özden S, Özden T, Akın A, Yıldız S (1987) DogaTu J Med Chem 11, 391–396
- 17 Yalçın I, Şener E, Özden T, Özden S, Akın A (1990) Eur J Med Chem 25, 705–708
- 18 Noyanalpan N, Şener E (1986) *FABAD J Pharm Sci* 11, 111–119
- 19 Yalçın İ, Şener E, Özden T (1985) J Fac Pharm Ankara 15, 69–78
- 20 Kanaoka Y, Hamada T, Yonemitsu O (1970) Chem Phar Bull 18, 587–590
- 21 Pollmann W, Schramm G (1964) Biochim Biophys Acta 80, 1–7
- 22 Phillips MA (1928) J Chem Soc 2393-2399
- 23 Tamamusi Y, Nagasawa H (1940) *J Pharm Soc Japan* 60, 127–132
- 24 Govindachari TR, Nagarajan K (1964) Indian J Chem 2, 169–170
- 25 Charles ES, Agrawal VK, Sharma S, Iyer RN (1979) Eur J Med Chem Chim Ther 14, 435–438
- 26 Shadomy S, Espinel A (1980) In: Manual of Clinical Microbiology. Am Soc Microbiol, Washington DC, pp 647