Acta Pharmaceutica Turcica
XLI (2) (78-81) 1999

SOME THIAZOLYLAMINOPYRROLE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY

BAZI TİYAZOLİLAMİNOPİROL TÜREVLERİ VE ANTİMİKROBİYAL AKTİVİTELERİ

ŞEREF DEMİRAYAK[1], AHMET Ç. KARABURUN[1], USAMA ABU MOHSEN[1], KIYMET GÜVEN[2]

[1]Anadolu University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry,
[2]Anadolu University, Faculty of Science, Department of Biology,
Eskişehir, TURKEY

In this study, some ethyl 1-(4-arylthiazol-2-yl)amino-2-methyl-5-aryl-1H -pyrrole-3-carboxylic acid derivatives were obtained by reacting 1-(2-methyl-3-carbethoxy-5-arylpyrrol-1-yl)thioureas with α-bromoacetophenone derivatives. The antibacterial and antifungal activities of the compounds were investigated and considerable activity was found.

Bu çalışmada, bazı 1-(2-metil-3-karbetoksi-5-arilpirol-1-il)tiyoüreler ve α-bromoasetofenon türevleri reaksiyona sokularak etil 1-(4-arilтiyazol-2-il)amino-2-metil-5-aril-1H-pirol-3-karboksilik asit türevleri elde edilerek, bunların antibakteriyel ve antifungal etkileri araştırıldı ve kayda değer aktivite elde edildi.

Keywords: *Thiourea; 1,4-Pentadione; Pyrrole; Thiazole; Antibacterial and antifungal activity*

Anahtar kelimeler: *Tiyoüre; 1,4-Pentadion; Pirol; Tiyazol; Antibakteriyel ve antifungal aktivite*

Introduction

A large number of pyrrole or thiazole derivatives isolated from microbial sources have antibiotic properties[1-3]. Several recent reports on antimicrobial activity of 1-substituted-4-aryl-1H-pyrrole-3-carboxylic acid derivatives, structurally resembling naturally found antibiotic pyrrolenitrin[4-8] and our previous studies on pyrrolylphenylthiazole derivatives[9], 1-aryloxyacetylaminopyrrole[10] and nitroimidazole substituted pyrrole derivatives[11] led us carry out further studies on 1-substituted-5-aryl-1H-pyrrole-3-carboxylic acid derivatives. Therefore we synthesised compounds **IIIa-l** to investigate their antibacterial and antifungal activities.

Materials and Methods

Melting points were determined by using a Gallenkamp apparatus and was uncorrected. Spectroscopic data were recorded on the following instruments , IR : Schimadzu 435 IR spectrophotometer, ^{1}H-NMR : Bruker DPX 400 NMR spectrometer, Jeol JNM-EX 90A FT NMR spectrometer.

1-Aryl-3-carbethoxy-1,4-pentadiones[4-8](**I**) were prepared according to the literature methods.

*1-(2-Methyl-3-carbethoxy-5-arylpyrrol-1-yl) thioureas **(IIa-d)***

A mixture of suitable **I** (10 mmol) and thiosemicarbazide (10 mmol) in acetic acid (50 ml) was stirred in a boiling water bath for 30 min. The solvent was evaporated under vacuum. The residue was suspended in water and neutralised with $NaHCO_3$ and the precipitate formed was filtered and crystallised from ethanol.

*Ethyl 1-(4-arylthiazol-2-yl)amino-2-methyl-5-aryl-1H-pyrrole-3-carboxylates **(IIIa-l)***

A mixture of suitable **II** (5 mmol) and 4-substituted α-bromoacetophenone (5 mmol) refluxed for 1h in ethanol. The solvent was evaporated and the residue was dissolved in water and neutralised with $NaHCO_3$. The precipitate was recrystallised from ethanol. Some characteristics of the compounds are shown in Table 1.

IIIa : **IR**(KBr)ν_{max}(cm^{-1}):3320(N-H), 1700(C=O), 1177-1060 (C-O). **^{1}H-NMR** σ(ppm): 1.37(3H, t), 2.42 (3H, s), 4.31 (2H, q), 6.70 (1H, s), 7.10-7.20 (3H, m), 7.20-7.28 (3H, m), 7.40-7.45 (4H, m).

Table 1. Some characteristics of the compounds

Comp.	R	R_1	R_2	Yield (%)	M.p. (°C)	Formulae	Mol. Mass (g)
IIa	H	--	--	84	206	$C_{15}H_{17}N_3O_2S$	303.38
IIb	H	--	--	86	224	$C_{16}H_{19}N_3O_2S$	317.41
IIc	H	--	--	90	196	$C_{16}H_{19}N_3O_3S$	333.41
IId	H	--	--	92	212	$C_{15}H_{16}ClN_3O_2S$	337.82
IIIa	H	H	H	92	118	$C_{23}H_{21}N_3O_2S$	403.50
IIIb	H	CH_3	H	90	171	$C_{24}H_{23}N_3O_2S$	417.53
IIIc	H	H	CH_3	91	147	$C_{24}H_{23}N_3O_2S$	417.53
IIId	H	H	Cl	85	176	$C_{23}H_{20}ClN_3O_2S$	437.94
IIIe	H	H	NO_2	89	192	$C_{23}H_{20}N_4O_4S$	448.50
IIIf	CH_3	H	H	93	148	$C_{24}H_{23}N_3O_2S$	417.53
IIIg	CH_3	H	Cl	88	159	$C_{24}H_{22}ClN_3O_2S$	451.97
IIIh	CH_3	H	NO_2	87	207	$C_{24}H_{22}N_4O_4S$	462.52
IIIi	OCH_3	H	H	86	130	$C_{24}H_{23}N_3O_3S$	433.52
IIIj	Cl	H	H	92	122	$C_{23}H_{20}ClN_3O_2S$	437.94
IIIk	Cl	H	Cl	90	169	$C_{23}H_{19}Cl_2N_3O_2S$	472.39
IIIl	Cl	H	NO_2	89	198	$C_{23}H_{19}ClN_4O_4S$	482.94

MASS : 404 (4%, M+1), 403 (2%, M^+),228 (100%).

IIIc : **IR**(KBr)ν_{max}(cm^{-1}):3325(N-H), 1690 (C=O), 1180-1062 (C-O). **^{1}H-NMR** σ(ppm): 1.36(3H, t), 2.24 (3H, s), 2.35 (3H, s), 4.35 (2H, q), 6.60 (1H, s), 6.70 (1H, s), 6.92 (2H, d j:8.01 Hz), 7.20-7.22 (3H, m), 7.26-7.30 (3H, m), 7.42-7.45 (2H, q), 11.0 (1H, bs).

IIIe : **IR**(KBr)ν_{max}(cm^{-1}):3323(N-H), 1683(C=O), 1169-1057 (C-O). **^{1}H-NMR** σ(ppm): 1.37(3H, t), 2.45 (3H, s), 4.31 (2H, q), 6.67 (2H, d j:8.43 Hz), 6.73 (1H, s), 6.97 (1H, s), 7.25-7.44 (5H, m), 8.08 (2H, d j:8.57 Hz),9.82 (1H, bs). **MASS** : 449 (6%, M^+), 248.9 (100%).

IIIf : **IR**(KBr)ν_{max}(cm^{-1}):3318(N-H), 1688(C=O), 1175-1059 (C-O). **^{1}H-NMR** σ(ppm): 1.31(3H, t), 2.42 (3H, s), 4.32 (2H, q), 6.70 (1H, s), 7.10-7.15(3H, m), 7.17-7.12 (2H, m), 7.39-7.41 (2H, m), 11.00 (1H, bs). **MASS** : 437 (10%, M^+), 134 (100%).

IIIg : **IR**(KBr)ν_{max}(cm^{-1}):3322(N-H), 1678(C=O), 1171-1056 (C-O).**^{1}H-NMR** σ(ppm): 1.30(3H, t), 2.42 (3H, s), 4.32 (2H, q), 6.69 (1H, s), 6.73 (1H, s),7.09 (2H, d j:8.46 Hz), 7.21 (2H, d j:6.82 Hz), 7.30-7.35 (4H, q).

IIIl: **IR**(KBr)ν_{max}(cm^{-1}):3327(N-H), 1703(C=O), 1170-1060 (C-O). **^{1}H-NMR** σ(ppm): 1.37(3H, t), 2.41 (3H, s), 3.72 (3H, s), 4.31 (2H, q), 6.63 (1H, s), 6.68 (1H, s), 6.76 (2H, d j:8.61 Hz), 7.10-7.20 (3H, m), 7.32 (2H, d j:8.59 Hz), 7.40-7.45 (2H, m), 11.0 (1H, bs).

Results and Discussion

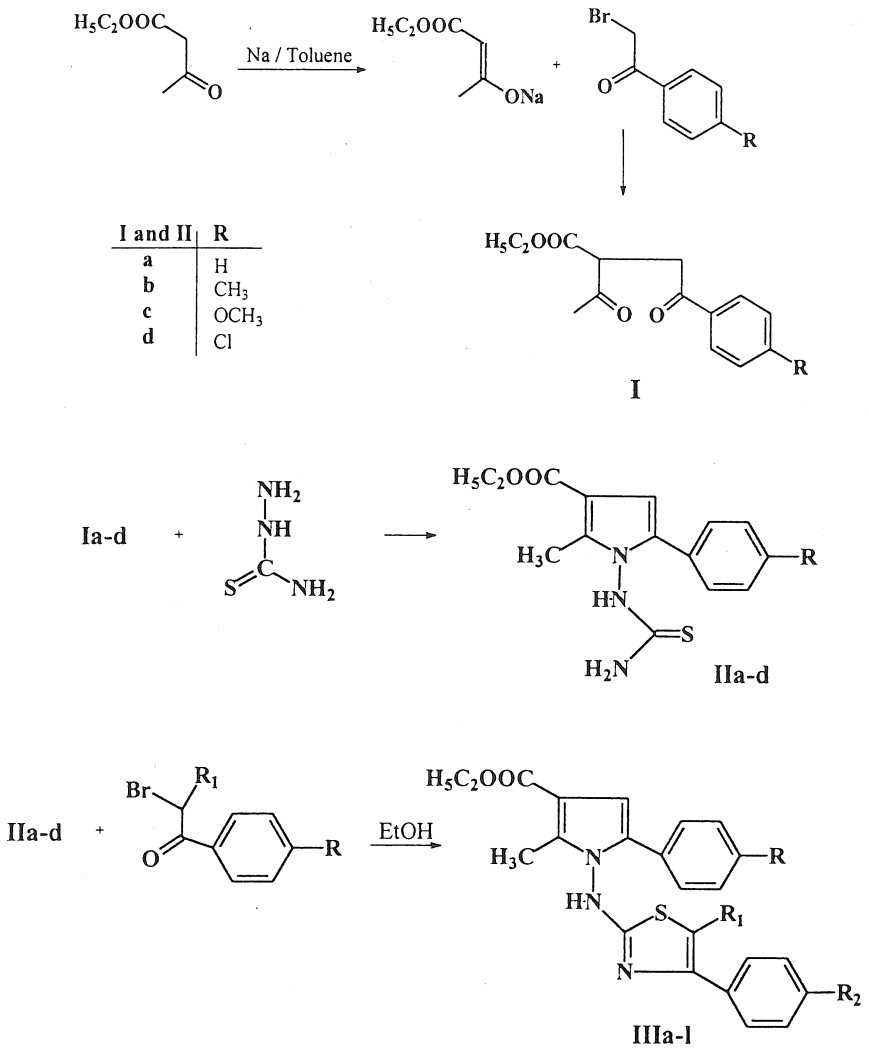
Chemistry

The pyrrole derivatives were prepared using the synthetic methods outlined in the Scheme. Diketone compounds **I**, used as starting materials, were obtained by reacting α-bromoacetophenone derivatives with the enolate of ethyl acetoacetate formed by sodium in dry toluene.

The synthesised compounds were characterised by elemental analyses and spectral data. In the IR spectra, N-H and ester C=O stretching bands characterised for all compounds were observed at about 3320 $cm^{-1}$and 1700 cm^{-1} respectively. In the NMR spectra, the signal due to the NH proton appeared at about 11 ppm. The other common groups for all compounds were methyl groups of pyrrole residue and ethyl groups of ester functions.

Pyrrolyl-2-methyl protons were observed as singlets at about 2.45-2.41 ppm respectively. Methyl and methylene

protons of carbethoxy residue were resonated at about 1.37-1.30 ppm and 4.35-4.31 ppm respectively. Microbiology antibacterial and antifungal activities of the compounds were determined using the tube dilution technique[12,13]. The MIC values were given in mg/mL. The standard bacteria and fungi strains used and MIC values are shown in Table 2. The stock solutions of the compounds were prepared in DMSO. Ketoconazol and chloramphenicol succinate were used as control antibacterial and antifungal agents. The standard bacteria and fungi strains used were *S. Aureus* ATCC 25923, *E. Coli* ATCC 25922, *P. Aureuginosa* ATCC 27853 and *C. Albicans* ATCC 10231. In consideration of the results we may conclude that some of our products have noticeable antibacterial and antifungal activities. The most sensitive microorganism for the control both for antifungal Ketoconazol and for antibiotic Chloramphenicol appeared to be Staphylococcus aureus. However, it was obviously observed that the antimicrobial activities of our compounds against this bacteria are lower. As there is not a big difference between the MIC



Scheme.Synthesis of the compounds

Table 2. Antibacterial activity of the compounds

Comp.	E.c.	M.l.	P.a.	S.a.	C.a.	C.g.
IIa	250	125	250	125	250	250
IIb	500	250	250	250	125	62.5
IIc	1000	125	250	125	1000	250
IId	250	125	250	250	125	125
IIIa	500	125	500	500	250	250
IIIb	500	500	500	500	1000	500
IIIc	500	500	500	500	500	500
IIId	500	250	500	500	250	250
IIIe	500	125	500	500	250	250
IIIf	500	500	500	500	1000	500
IIIg	500	500	500	500	500	500
IIIh	500	250	500	500	250	250
IIIi	500	125	500	500	250	250
IIIj	500	500	500	500	1000	500
IIIk	500	500	500	500	500	500
IIIl	500	250	500	500	250	250
A	250	125	125	7.81	125	62.5
B	250	125	125	7.81	250	250

A : Ketoconazol
B : Chloramphenicol succinate
E.c. : Escherichia coli B
M.l. : Micrococcus luteus NRRL B-4375
P.a. : Pseudomonas aeroginosa NRRL B-23
S.a. : Staphylococcus aureus NRRL B-767
C.a. : Candida albicans,
C.g. : Candida globrata

values of most of our compounds and the control antibiotics, we may conclude that the synthesised compounds have remarkable activity. As far as the antimicrobial activities of our compounds are concerned no significant difference was observed due to different substituents.

References

1. Jones, R.A., Bean, G.P.: The Chemistry of Pyrroles, Academic Press, London 1977
2. Jones, R.A.: Pyrroles Part II, The Chemistry of Heterocyclic Comp., J. Wiley and Sons, New York 1992
3. Metzgen, J.V., Vincent, E.J., Chouteau, J., Mille, G., "Properties and reactions of thiazole", The Chem. Of Heterocyclic Comp. Ed., J.V. Metzger, J. Wiley and Sons, NY 1979
4. Flacchioni, G., Porretta, G.C., Scalzo, M.: Farmaco 34, 987 (1979)
5. Scalzo, M., Porretta, G.C., Chimenti, F., Casanova, M.C., Panico, S., Simonetti, N.: Farmaco 43, 665 (1988)
6. Scalzo, M., Porretta, G.C., Chimenti, F., Bolasco, A., Casanova, M.C., Simonetti, N.: Farmaco 43, 677 (1988)
7. Scalzo, M., Biavia, M., Cerreto, F., Villa, A.: Farmaco 47, 1047, (1992)
8. Cerreto, F., Scalzo, M., Villa, A.: Farmaco 48, 1735, (1993)
9. Demirayak, Ş., Benkli, K., Sezer, C., Erdeniz, H.: Acta Pharm. Turc. 39, 133 (1997)
10. Demirayak, Ş., Karaburun, A.Ç., Kiraz, N.: Acta Pharm. Turc. 40, 73 (1998)
11. Demirayak, Ş., Karaburun, A.Ç., Kiraz, N.: Eur. J. Med. Chem. 34, 275 (1999)
12. Finegold, S.M., Martin, W.J., Scott, E.G.: Bailey and Scott's Diagnostic Microbiology; The C.V.Mosby Company, Saint Louis 1978
13. Mc Ginnis, M.R., Rinaldi, M.G.; Antifungal drugs; Mechanism of action, drug resistance, susceptibility testing and assays of activity in biological fluids, Ed. V. Lorian, Antibiotics in Laboratory Medicine Third Ed., Williams and Wilkins, London, Los Angeles, 198, 1991

Accepted :18.11.1998