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SYNTHESIS OF SOME 4-PYRROLYLPHENYLTHIAZOLE DERIVATIVES AND INVESTIGATION OF THEIR ANTIMICROBIAL ACTIVITIES

BAZI 4-PİROLİLFENİLTİYAZOL TÜREVLERİNİN SENTEZİ VE ANTİMİKROBİYAL ETKİLERİNİN ARAŞTIRILMASI

Ş. DEMİRAYAK[1], K. BENKLİ[1], C.SEZER[1], H.ERDENİZ[2]

[1]University of Anadolu, Faculty of Pharmacy, Dept. of Pharmaceutical Chemistry, Eskişehir, Turkey
[2]University of Istanbul, Faculty of Medicine, Dept. of Microbiology, Istanbul, Turkey

In this study, some 2-substituted 4-[4-(pyrrol-1-yl)phenyl] thiazole derivatives were obtained reacting some 1,4-dicarbonyl compounds and 2-substituted 4-(4-aminophenyl)thiazoles. The latters were prepared by hydrolyzing of 2-substituted 4-(4-acetylaminophenyl) thiazoles. The antibacterial and antifungal activities of the pyrrole compounds were investigated and no considerable activity was obtained.

Bu çalışmada, 4-(α–kloroasetil)asetanilid ile tiyoasetamid veya etiyonamid'in reaksiyona sokulmasıyla elde edilen 2-sübstitüe 4-(4-asetilaminofenil)tiyazol türevleri hidroliz edilerek 2-sübstitüe 4-(4-aminofenil)tiyazol türevleri sentezlenmiştir. Bu amino türevleriyle bazı 1,4-dikarbonil bileşiklerinin asetik asid içerisinde ısıtılmasıyla 2-sübstitüe 4-(4-pirolilfenil)tiyazol türevlerine ulaşılmıştır. Pirol türevi bileşiklarin antibakteriyel ve antifungal aktiviteleri araştırılmış ve kaydadeğer bir etki elde edilememiştir.

Keywords: *Pyrrole; Thiazole; Antibacterial; Antifungal effects*

Anahtar kelimeler: *Pirol; Tiyazol; Antibakteriyel ; antifungal aktivite*

Introduction

The chemistry of pyrrole has been the subject of investigations by an ever increasing number of researchers since the discovery that the pyrrole ring was a part of haemin and of chlorophyll molecules. A large number of pyrrole derivatives having antibiotic properties have been isolated from microbial sources (1,2).

Thiazole nucleus is also found in a variety of naturally occuring products which exert varied pharmacological effects(3). These observations urged us to synthesize some 4-[4-(pyrrol-1-yl)phenyl]thiazole derivatives and to test their antimicrobial activities.

Materials and Methods

Melting points were determined by using a Gallenkamp apparatus and are uncorrected. Spectroscopic data were recorded on the following instruments: IR: Shimadzu IR 435 spectrophotometer; ^{1}H-NMR: Bruker DPX 400 and Jeol 60 NMR spectrometers; MS: VG Platform mass spectrometer. Analyses for C, H, N were within 0.4% of the theoretical values. 4-(α-Chloroacetyl)-acetanilide(4), 1-phenyl-3-carbethoxy-1,4-pentadione(5), compounds ***3a*** and ***4a*** (6)were prepared according to the methods reported in the literature. Some characteristics of the compounds are reported in Table 1.

*2-Substituted 4-(4-acetylaminophenyl)thiazoles, **3a,b** General Procedure*

A mixture of ***2*** (5 mmol) and an appropriate thioamide, ***1a*** or ***1b***, in ethanol (100 ml) was refluxed for 2h. The cooled solution was neutralized with $NaHCO_3$. The precipitate formed was filtered, washed with water and crystallized from ethanol.

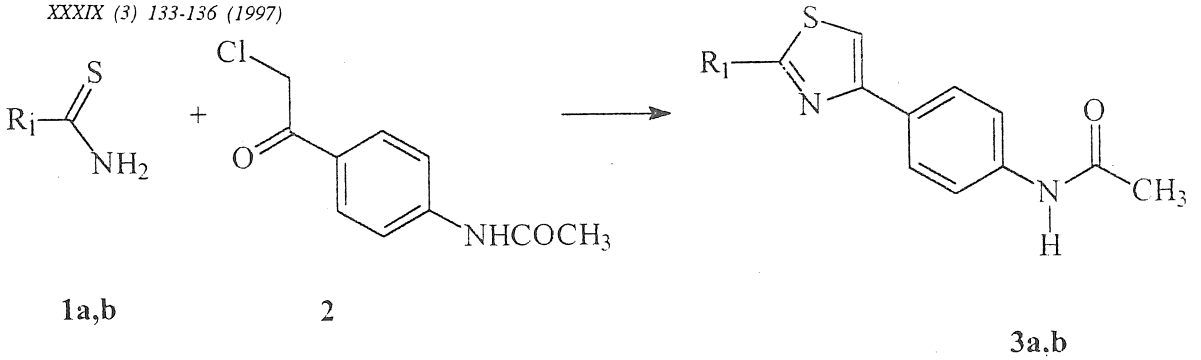
3a : IR (KBr, cm^{-1}) 3399 (N-H), 1655 (C=O), 1613-1471 (C=N, C=C); ^{1}H-NMR (60MHz, DMSO-d_6, σ ppm) 2.05 (3H, s, $COCH_3$), 2.65 (3H, s, thiazole-2-CH_3), 7.52-8.05 (5H, m, Ar-H and thiazole-5-H), 10 (1H, s, N-H).

3b : IR (KBr, cm^{-1})3292 (N-H), 1666 (C=O), 1596-1468 (C=N, C=C); ^{1}H-NMR (90 MHz, DMSO-d_6, σ ppm)1.30 (3H, t, CH_2-CH_3), 2.05 (3H, s, $COCH_3$), 2.90 (2H, q, CH_2-CH_3), 5.50 (2H, brs, NH_2), 6.60 (2H, d, Ar-H), 7.50-7.80 (4H, m, Ar-H), 7.90 (1H, s, thiazole-5-H, 8.46 (1H, d, pyridyl-6-H), 10 (1H, brs, N-H).

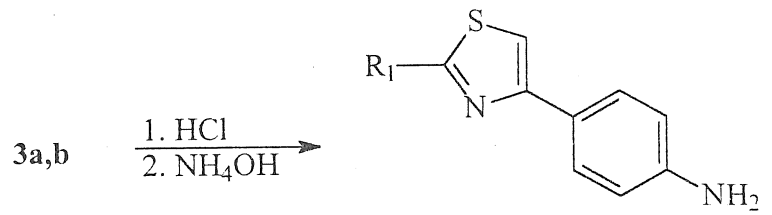
2- Substituted 4-(4-amionphenyl)thiazoles, 4a,b General Procedure

3a or ***3b*** (10 mmol) was dissolved in the mixture of ethanol (50 ml) and 4N HCl (50 ml). The solution obtained was refluxed for 1 h. The cooled solution was neutalized with NH_4OH solution. The precipitate was crystallized from diluted ethanol.

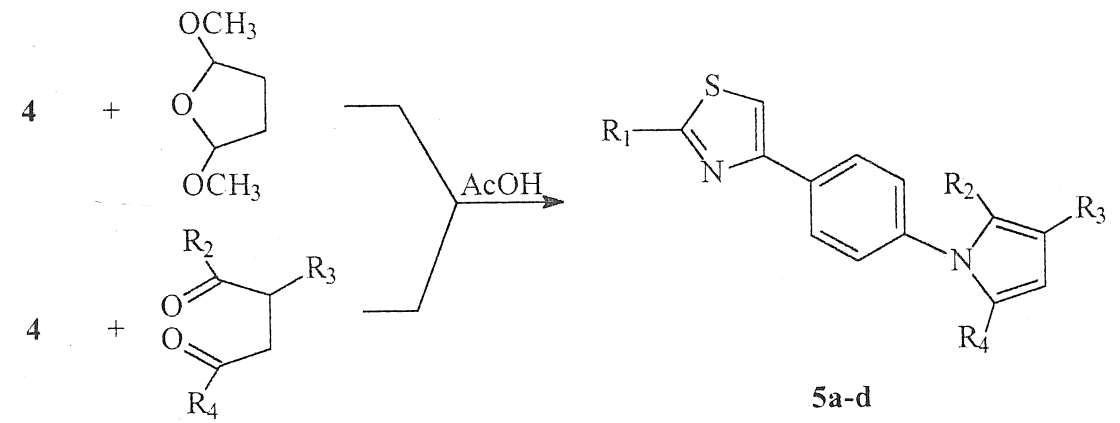
4a : IR (KBr, cm^{-1}) 3490, 3322, 3203 (N-H), 1634-1468 (C=N=, C=C), 826 (1,4 disubstituted benzene); ^{1}H-NMR 60MHz, DMSD-d_6, σ ppm) 2.63 (3H, s,



1a,b 2 3a,b



3a,b 4a,b



5a-d

thiazole-2-CH_3), 4.95 (2H, s, NH_2), 6.55 (2H, d, Ar-H), 7.32 (1H, s, thiazole,5-H), 7.58 (2H, d, Ar-H).

4b : IR (KBr, cm^{-1}) 3428, 3320 (N-H), 1644-1460 (C=N, C=C), 826 (1,4-disubstituted benzene); ^{1}H-NMR (400 MHz, DMSO-d_6, σppm) 1.28 (3H, t, CH_2-$C\underline{H}_3$), 2.85 (2H, q, $C\underline{H}_2$-CH_3), 5.34 (2H, brs, NH_2), 6.66 (2H, d, J: 8.32 Hz, Ar-H), 7.65-7.79 (4H, m, Ar-H, pyridyl-3-H and 5-H), 7.89 (1H, s, thiazole-5-H), 8.60 (1H, d, j:5.1 Hz, pyridyl-6-H).

-Substituted 4-[4-(pyrrol-1-yl)phenyl]thiazoles, 5a-d General Procedure

A mixture of *4a* or *4b* (5 mmol) and an appropriate dicarbonyl compound (5.2 mmol) in acetic acid (25 ml) was stirred in water bath for 30 min. The solvent 2 was evaporated under vacuum. The residue was dissolved in water. The solution was neutralized with $NaHCO_3$. The precipitate was filtered and crystallized from ethanol.

5a : IR (KBr, cm^{-1}) 1622-1450 (C=N, C=C); ^{1}H-NMR (400 MHz, DMSO-d_6, σppm) 2.37 (3H, s, thiazole- 2-CH_3), 6.29 (2H, s, pyrrole-3, 4-H), 7.42 (2H, s, pyrrole-2,5-H) 7.63 (2H, d, j:12Hz, Ar-H), 7.93 (1H, s, thiazole-5-H), 7.63 (2H, d, j:12Hz, Ar-H), 7.93 (1H, s, thiazole-5-H), 8.01 (2H, d, j:8.25 Hz, Ar-H); EI-MS: m/z :242 (M+2, 6%), 241.2 (M+1, 15%), 240.1 (M, 100%), 198.6, 170.9, 167, 153.9, 139.

5b: IR (KBr, cm^{-1}) 1600-1470 (C=N, C=C); ^{1}H-NMR (400 MHz, DMSO-d_6, σppm) 1.99 (6H, s, pyrrole-2,5-$C\underline{H}_3$), 2.73 (3H, s, thiazole-2-CH_3), 5.81 (2H, s, pyrrole-3,4-H), 7.30 (2H, d, j:7.74 Hz, Ar-H), 8.00

Table 1. Some characteristics of the compounds

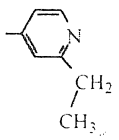
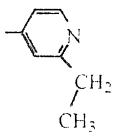
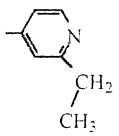
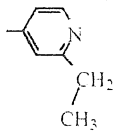
Comp.	R_1	R_2	R_3	R_4	M.p. (°C)	Yield (%)	Mol. Formula (Mol. Weight)
3b		-	-	-	194	58	-
4b		-	-	-	132	67	-
5a	$-CH_3$	-H	-H	-H	162	48	$C_{14}H_{12}N_2S$ (240.3)
5b	$-CH_3$	$-CH_3$	-H	$-CH_3$	105	65	$C_{16}H_{16}N_2S$ (268.4)
5c		-H	-H	-H	149	56	$C_{20}H_{17}N_3S$ (331.4)
5d		$-CH_3$	$-CO_2C_2H_5$	$-C_6H_5$	145	55	$C_{30}H_{27}O_2S$ (451.6)

Table2. The MIC values of compounds ***5a-d***

Comp.	S. aureus ATCC 25923	E.coli ATCC 25922	P.aeruginosa ATCC27.853	C. albicans ATCC 10231
5a	125	62.5	62.5	125
5b	125	62.5	62.5	62.5
5c	>125	>125	>125	62.5
5d	125	62.5	62.5	62.5
Ceftriaxone	2	0.03	8	2
Clotrimazole	-	-	-	2

(1H, s, thiazole-5-H), 8.05 (2H, d, j:7.88 Hz, Ar-H).
5c : IR (KBr, cm^{-1}) 1620-1453 (C=N, C=C), 849 (1,4-disubstituted benzene); ^{1}H-NMR (400 MHz, DMSO-d_6, σppm) 1.30 (3H, t, $-CH_2-CH_3$), 2.88 (2H, q, $-CH_2-CH_3$), 6.31 (2H, s, pyrrole-3,4-H), 7.46 (2H, s, pyrrole-2,5-H), 7.71 (2H, d, j:8.52 Hz, Ar-H), 7.79 (1H, d, j:5.03 Hz, pyridyl-5-H), 7.85 (1H, s, pyridyl-3-H), 8.14 (2H, d, j: 8.52 Hz, Ar-H), 8.35 (1H, s, thiazole-5-H), 8.64 (1H, d, j:5.15 Hz, pyridyl-6-

s, thiazole-5-H), 8.64 (1H, d, j:5.15 Hz, pyridyl-6-H).
5d: IR (KBr, cm^{-1}) 1681 (C=O), 1597-1444 (C=N, C=C), 1233, 1097 (C-O); ^{1}H-NMR (400 MHz, DMSO-d_6, σ ppm) 1.23-1.32 (6H, m, two CH_2-CH_3), 2.37 (3H, s, pyrrol-2-CH_3), 2.87 (2H, q, pyridyl-2-CH_2-), 4.24 (2H, q, -OCH_2-), 6.71 (1H, s, pyrrol-4-H), 7.10-7.22 5H, m, pyrrol-5-C_6H_5), 7.38 (2H, d, j:8.16 Hz, Ar-H), 7.78 (1H, d, j:5.0 Hz, pyridyl-5-H), 7.85 (1H, s, pyridyl-3-H), 8.15 (2H, d, j:8.21 Hz, Ar-H), 8.43 (1H, s, thiazole-5-H), 8.63 (1H, d, j:5.07 Hz, pyridyl-6-H); EI-MS m/z: 495.4 (M+2, 10%), 494.4 (M+1, 35%), 493.4 (M, 100%), 464.3, 448.3, 420, 368.2, 291.1, 286, 273, 265.1, 246.7, 232, 223.7.

Determination of the antimicrobial activity

Antibacterial and antifungal activities of the compounds ***5a-d*** were determined using the tube dilution technique (7-9). The stock solutions of the compounds were prepared in DMSO. Ceftriaxone and clotrimazole were used as control antibacterial and antifungal agents. The MIC values are given as μg/ml. The standard bacteria and fungi strains used and MIC values are shown in Table 2.

Results and Discussion

The first group of the compounds ***3a,b*** was obtained by reacting 4-(α-chloroacetyl) acetanilide and thioacetamide or ethionamide (2-ethyl-4-thiocarboxamidopyridine). The reaction is an application of the Hantzsch thiazole synthesis (1). In the second step, the acetamido group of the compounds ***3a, b*** was converted to amine by hydrolysing in hydrochloric acid solution. The last step involves Paal-Knorr pyrrole synthesis (3). The compounds ***5a-d*** were synthesized by heating the amine compounds ***4a,b*** and appropriate 1,4-dicarbonyl compounds.

The newly synthesized compounds were characterized by elemental analyses, IR, ^{1}H-NMR and MASS spectral data. Characteristic IR absorption band of the amide carbonyl moiety of the compounds ***3a,b*** at about 1660 cm^{-1} were absent in the spectra of the hydrolyzed products ***4a,b*** and pyrrole compounds ***5a-d***. Similarly, the strong stretching bands at about 3400-3200 cm^{-1} originated from NH groups of the compounds ***3*** and ***4*** are no longer present in the IR spectra of the compounds ***5a-d***. In the ^{1}H-NMR spectra, the signals due to 5-H protons on the thiazole ring which are common in all compounds are shown as singlets at about 7.80 ppm. The protons of amide residue of the compounds ***3a,b*** are observed as broad singlets at about 10 ppm. The protons of amino group which formed after hydrolyzing of the amid group resonate as broad singlets as well at about 5 ppm. After cyclizing to pyrrole rings, the signals due to NH are no longer present in the compounds ***5a-d***. Although 3-H protons of the pyridyl rings overlap with the other aromatic protons. 5,6-H Protons are observed as dublets. However, these dublets are easily distinguished with their characteristic j values (i.e. 5 Hz) from the other doublets.

Molecular ions corresponding to M^+ are observed in the EI-MS spectra of the compounds ***5a*** and ***5d***. M+1 is also obtained from ES-MS spectra of the compounds ***5d***.

Antibacterial and antifungal activities of the compounds under investigation were determined using tube dilution technique (7-9). Although no considerable antibacterial and antifungal effect could be observed, the most effective MIC value was found as 62.5 μg/ml.

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