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SYNTHESIS AND ANTIBACTERIAL AND ANTIFUNGAL EVOLUTION OF SOME ETHYL 1-ARYLOXYACETYLAMINO-5-ARYLPYRROLE-3-CARBOXYLIC ACID DERIVATIVES

BAZI ETİL 1-ARİLOKSİASETİLAMİNO-5-ARİLPİROL-3-KARBOKSİLİK ASİD TÜREVLERİNİN SENTEZLERİ VE ANTİBAKTERİYEL VE ANTİFUNGAL ETKİ YÖNÜNDEN DEĞERLENDİRİLMELERİ

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In this study, some ethyl 1-aryloxyacetylamino-2-methyl-5-aryl-1H-pyrrole-3-carboxylic acid derivatives were obtained by reacting some aryloxyacetylhydrazide and 1-aryl-3-carbethoxy-1,4-pentadione derivatives. The antibacterial and antifungal activities of the pyrrole compounds were investigated and no considerable activity was obtained.

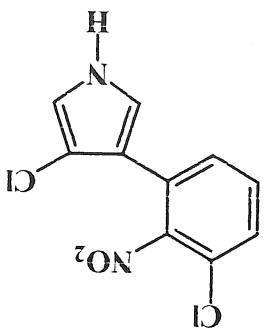
Bu çalışmada, bazı ariloksiasetilhidrazidleri ve 1-aril-3-karbetoksi-1,4-pentadion türevleri reaksiyona sokularak bazı etil 1-ariloksiasetilamino-2-metil-5-aril-1H-pirol-3-karboksilik asid türevleri elde edilerek antibakteriyel ve antifungal etkileri araştırıldı ve kayda değer bir etki elde edilemedi.

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

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

Introduction

A large number of pyrrole derivatives isolated from microbial sources have antibiotic properties (1,2). It's known that some 1-substituted-4-aryl-1H-pyrrole-3-carboxylic acid derivatives, structurally resembling naturally found antibiotic pyrrolenitrin, are considered as potential antifungal agents(3,4). Several 1,4- or 1,5-diarylpyrrole-3-carboxy derivatives were prepared and their antifungal activities and their structure-activity relationships were examined (5,7). In this study, as an extension of our previous works on pyrrolylphenylthiazole derivatives(8), some ethyl 1-aryloxy-acetylamino-2-methyl-5-aryl-1H-pyrrole-3-carboxylic acid derivatives were synthesised to investigate their antimicrobial activities.



Pyrrolenitrin

Materials and Methods

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

Aryloxyacetylhydrazide(9,10) and 1-phenyl-3-carbethoxy-1,4-pentadione(3,5) were prepared according to the literature methods.

Ethyl 1-aryloxyacetylamino-2-methyl-5-aryl-1H-pyrrole -3-carboxylates

General Method

A mixture of a suitable **I** (5 mmol) and **II** (5 mmol) in acetic acid was refluxed for 30 min. The cooled mixture was poured into ice-water and neutralised with sodium carbonate. The precipitate formed was filtered and recrystallised from ethanol. Some characteristics of the compounds are shown in the Table.

1: IR(KBr)υ_{max} (cm^{-1}): 3320 (N-H), 1690 (C=O, ester), 1656 (C=O, amide), 1177, 1061 (C-O). ^{1}H-NMR δ(ppm): 1.28(3H, t), 2.36(3H, s), 4.22(2H, q), 4.85(2H, s), 6.62(1H, s), 7.05-7.50(10H, m), 11.50 (1H, s).

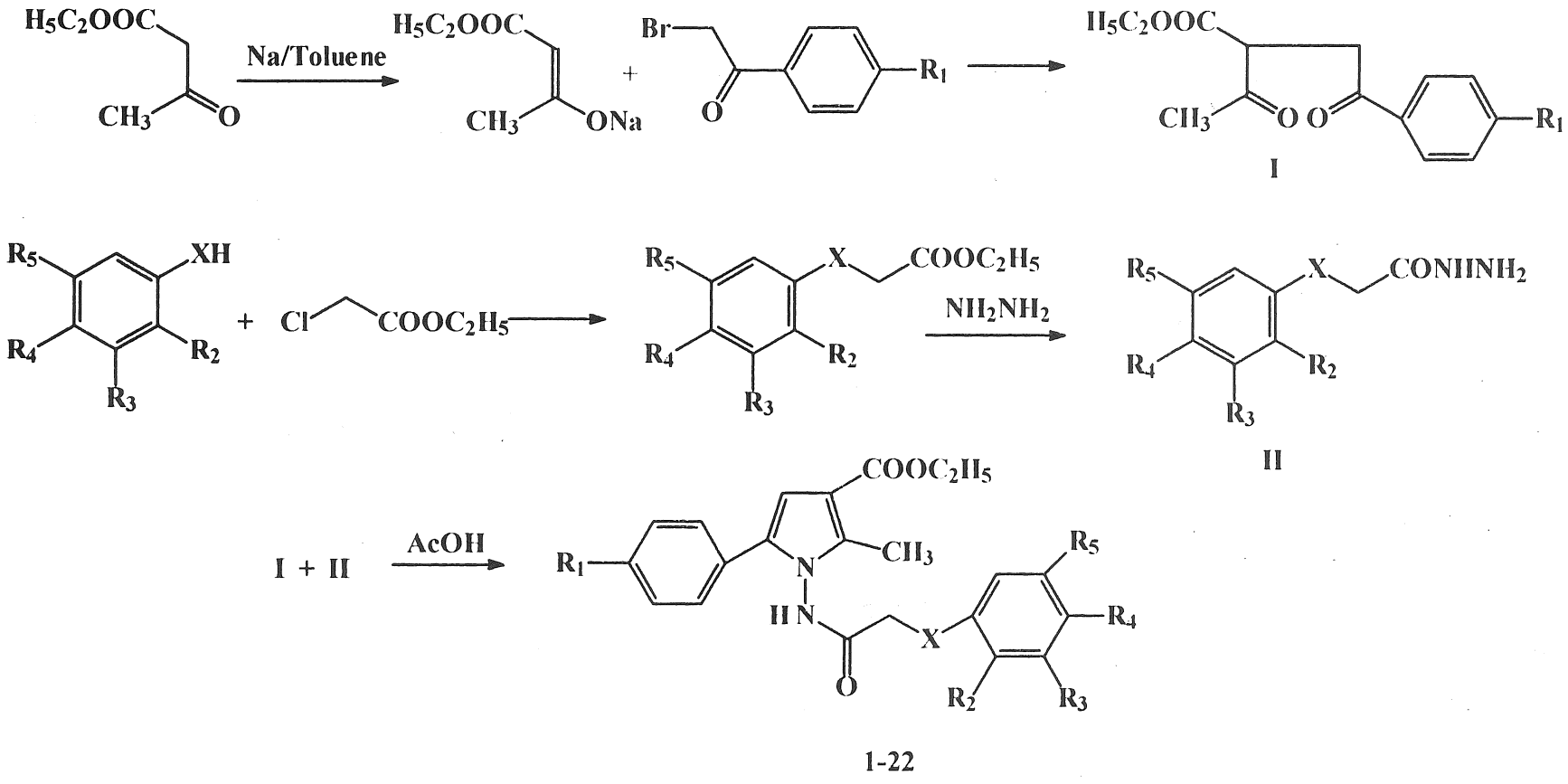
3: IR(KBr)υ_{max} (cm^{-1}): 3322 (N-H), 1687 (C=O, ester), 1655 (C=O, amide), 1180, 1060 (C-O). ^{1}H-NMR δ(ppm): 1.31(3H, t), 2.35(3H, s), 2.53(3H, s), 4.21(2H, q), 4.85(2H, s), 6.60(1H, s), 7.03-7.46(9H, m), 11.74 (1H, s).

8: IR(KBr)υ_{max} (cm^{-1}): 3354 (N-H), 1702 (C=O, ester), 1655 (C=O, amide), 1180, 1060 (C-O). ^{1}H-NMR δ(ppm): 1.30(3H, t), 2.35(3H, s), 4.23(2H, q), 4.88(2H, s), 6.60(1H, s), 7.09(2H,s), 7.22(1H, s), 7.29-7.43(5H,

Table 1. Some characteristics of the compounds

Comp.	X	R_1	R_2	R_3	R_4	R_5	Yield %	M.P. (°C)	Formulae	Mol. Mass
1	O	H	H	H	H	H	89	139-140	$C_{22}H_{22}N_2O_4$	378.42
2	O	H	CH_3	H	H	H	90	132-133	$C_{23}H_{24}N_2O_4$	392.44
3	O	H	H	H	CH_3	H	92	141-142	$C_{23}H_{24}N_2O_4$	392.44
4	O	H	Cl	H	H	H	93	125-126	$C_{22}H_{21}N_2O_4Cl$	412.86
5	O	H	H	H	Cl	H	87	150-151	$C_{22}H_{21}N_2O_4Cl$	412.86
6	O	H	Cl	H	Cl	H	94	174-175	$C_{22}H_{20}N_2O_4Cl_2$	447.31
7	O	H	H	Cl	Cl	H	92	149-150	$C_{22}H_{20}N_2O_4Cl_2$	447.31
8	O	H	H	Cl	H	Cl	91	155-156	$C_{22}H_{20}N_2O_4Cl_2$	447.31
9	O	H	H	H	NO_2	H	95	192-193	$C_{22}H_{21}N_3O_6$	423.41
10	S	H	H	H	H	H	78	112-113	$C_{22}H_{22}N_2O_3S$	394.48
11	O	Cl	H	H	H	H	87	163-164	$C_{22}H_{21}N_2O_4Cl$	412.86
12	O	Cl	H	H	CH_3	H	88	134-135	$C_{23}H_{23}N_2O_4Cl$	426.88
13	O	Cl	H	H	Cl	H	93	156-157	$C_{22}H_{20}N_2O_4Cl_2$	447.31
14	O	Cl	Cl	H	Cl	H	92	151-152	$C_{22}H_{19}N_2O_4Cl_3$	481.76
15	O	Cl	H	Cl	Cl	H	95	154-155	$C_{22}H_{19}N_2O_4Cl_3$	481.76
16	O	Cl	H	H	NO_2	H	95	153-154	$C_{22}H_{20}N_3O_6Cl$	457.85
17	O	NO_2	H	H	H	H	79	162-163	$C_{22}H_{21}N_3O_6$	423.41
18	O	NO_2	CH_3	H	H	H	82	175-176	$C_{23}H_{23}N_3O_6$	437.43
19	O	NO_2	H	H	CH_3	H	82	186-187	$C_{23}H_{23}N_3O_6$	437.43
20	O	NO_2	Cl	H	H	H	87	171-172	$C_{22}H_{20}N_3O_6Cl$	457.85
21	O	NO_2	H	H	Cl	H	93	220-221	$C_{22}H_{20}N_3O_6Cl$	457.85
22	O	NO_2	Cl	H	Cl	H	91	179-180	$C_{22}H_{19}N_3O_6Cl_2$	492.30

m), 11.54 (1H, s).
13: IR(KBr)υ_{max} (cm^{-1}): 3320 (N-H), 1688 (C=O, ester), 1654 (C=O, amide), 1176, 1058 (C-O). ^{1}H-NMR δ(ppm): 1.29(3H, t), 2.38(3H, s), 4.22(2H, q), 4.86(2H, s), 6.60(1H, s), 7.06-7.53(8H, m), 11.60 (1H, s).
16: IR(KBr)υ_{max} (cm^{-1}): 3325 (N-H), 1695 (C=O, ester), 1662 (C=O, amide), 1521, 1360 (N=O), 11.76, 10.58 (C-O). ^{1}H-NMR δ(ppm): 1.32(3H, t), 2.40(3H, s), 4.20(2H, s), 6.66(1H, s), 7.04(2H, d, j:8.79 Hz), 7.29(2H, d, j:8.75 Hz), 7.34(2H, d, j:8.96 Hz), 8.24 (2H, d, j:8.96 Hz), 11.68 (1H, s).
16: IR(KBr)υ_{max} (cm^{-1}): 3317 (N-H), 1702 (C=O, ester), 1660 (C=O, amide), 1530, 1366 (N=O), 11.85, 10.66 (C-O). ^{1}H-NMR δ(ppm): 1.30(3H, t), 2.39(3H, s),



Scheme. Synthesis of the compounds

2.57(3H, s), 4.23(2H, s), 493(2H, q,j:15.15Hz j:18.32Hz j: 15.05Hz), 6.90(1H, s), 6.95-7.46(4H, m), 7.76 (2H, d, j:8.68 Hz), 8.17 (2H, d, j:8.75 Hz), 11.74 (1H, s).
16: IR(KBr)υ_{max} (cm^{-1}): 3328 (N-H), 1705 (C=O, ester), 1659 (C=O, amide), 1536, 1356 (N=O), 11.75, 10.70 (C-O). ^{1}H-NMR δ(ppm): 1.29(3H, t), 2.39(3H, t), 4.24(2H, s), 4.93(2H, s), 6.91(1H, s), 7.35-7.43(2H, m), 7.59(1H, s), 7.76(2H, d, J:8.60 Hz), 8.20(2H, d, j:8.62 Hz), 11.80(1H, s).

Determination of the antimicrobial activity

Antibacterial and antifungal activities of the compounds **1-22** were determined using the tube dilution technique(11,12). The stock solutions of the compounds were prepared in DMSO. Cefriaxone and clotrimazole were used as control antibacterial and antifungal agents. The standard bacteria and fungi strains used are S.Aureus ATCC 25923, E.Coli ATCC 25922, P.Aeruginosa ATCC 27853 and C.Albicans ATCC 10231.

Results and Discussion

Chemistry

The pyrrole derivatives were prepared using the synthetic methods outlined in Scheme 1.

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.

Aryloxyacetylhydrazide derivatives **II**, as depicted in Scheme, were obtained by reacting hydrazine with ethyl aryloxyacetate, which was gained by the reaction of phenol derivatives with ethyl chloroacetate.

Paal-Knorr pyrrole synthesis conditions were performed for the synthesis of the pyrrole derivatives. To accomplish this **I** and **II** were heated in acetic acid.

The synthesised compounds were characterised by elemental analyses and spectral data. In the IR spectra, N-H, ester C=O and amide C=O stretching bands characterised for all compounds were observed at about1754-1717 cm^{-1}, 1705-1688 cm^{-1} and 1662-1654 cm^{-1} respectively. In the NMR spectra, the signal due to the NH proton appeared at about 11.80-11.60 ppm. The other common groups for all compounds are methyl groups of pyrrole residue, methylene groups of aryloxyacetyl residue and ethyl groups of ester functions.

Pyrrolyl-2-methyl and methylene protons of aryloxymethyl residue were observed as singlets at about 2.40-2.35 ppm and 4.93-4.85 ppm respectively. Methyl and methylene protons of carbethoxy residue were resonated at about 1.32-1.28 ppm and 4.24-4.20 ppm respectively.

Microbiology

Antibacterial and antifungal activities of the compounds were determined by using the tube dilution technique. In consideration of the high antifungal activity of some of the pyrrole derivatives in the literature (3,7), we tested the antifungal activity of our compounds, however it was found that they were entirely ineffective.

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