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SYNTHESIS OF SOME 6,7-DISUBSTITUTED IMIDAZO[4,5-g]QUINOXALINE DERIVATIVES AS POSSIBLE ANTIMICROBIALS

ANTİMİKROBİAL ETKİ BEKLENEN BAZI 6,7-DİSÜBSTİTÜE İMİDAZO[4,5-G]KİNOKSALİN TÜREVLERİNİN SENTEZİ

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In this study, some 6,7-disustituted imidazo [4,5-g]quinoxaline derivatives were synthesized by reacting 5,6-diaminobenzimidazole and some 1,2-dicarbonyl compounds. The antibacterial and antifungal activities of the compounds were examined.

Bu çalışmada, 5,6-diaminobenzimidazol değişik 1,2-dikarbonil türevleriyle reaksiyona sokularak 6,7-disübstitüe imidazo[4,5-g] kinoksalin türevleri sentezlendi. Elde edilen bileşiklerin antibakteriyel ve antifungal etkileri tüp dilüsyon yöntemiyle incelendi.

Keywords: *Imidazo-quinoxaline; Antibacterial; Antifungal effects*

Anahtar kelimeler:*İmidazo-kinoksalin; Aktibakteriyel; Antiifungal aktivite*

Introduction

The presence of imidazole or benzimidazole moiety in various biologically active drugs led the many investigators to study the properties of new imidazole or benzimidazole derivatives(1-3).

It is also well known that quinoxaline derivatives possess marked biological activity such as antimicrobial and anticancer activities(4).

Motivated by the above observations and as an extension of our previous works on pyrido or pyrazino condensed benzimidazoles, we report here the synthesis and antibacterial and antifungal testing of some 6,7-disubstituted imidazo[4,5–g]quinoxaline derivatives.

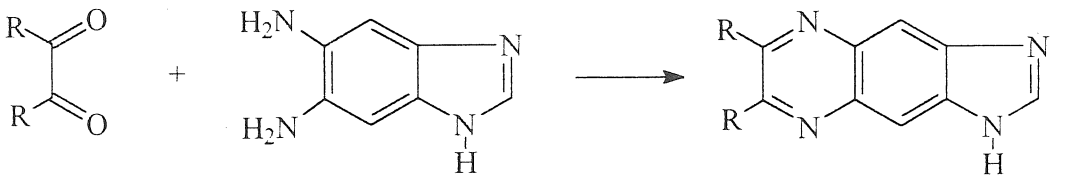
Materials and Medhods

Melting points were determined by using an Electrohermal Melting Point apparatus and are uncorrected. Spectroscopic data were recorded on the following instruments: IR:Shimadzu IR 435 spectrophotometer; ^{1}H-NMR: Jeol 60 NMR spectrometer. Analyses for C, H, N were within 0.4% of the theoretical values. The tin complex of 5,6-diaminobenzimidazole was prepared from 5,6-dinitrobenzimidazole which is obtained by nitration of benzimidazole as described in previous study(5). Benzil derivatives, furil and thenil were obtained by oxydating the corresponding benzoines, furoine and thenoine derivatives. Phenantro-9,10-dione was prepared from phenantrene according to "organic synthesis" procedure(6).

6,7-Disubstituted Imidazo[4,5–g]quinoxalines
General procedure

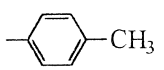
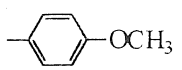
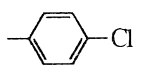
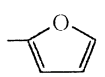
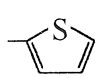
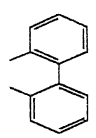
A mixture of 5,6-diaminobenzimidazole tin complex (3 g) and an appropriate 1,2-dion derivative (5 mmol) (for the compound 1, excess CH_3COONa was added) was refluxed in ethanol (100 ml) for 3 hr. 5 ml of NH_3 was added into the mixture. The precipitate was discarded. The filtrate was evaporated to dryness. The residue was crystallized from ethanol. Some characteristics of the compounds were given in Table 1.

1:IR (KBr, cm^{-1}): 3380-2450 (N-H), 1635-1401 (C=N, C=C). **^{1}H-NMR** (DMSO-d_6) σ (ppm) :8.42 (2H, s, $C_{4,9}$-H), 8.70 (1H, s, C_2-H), 8.95 (2H, s, $C_{6,7}$-H).



1-8

Table 1 Some characteristics of the compounds

Compound	R	Yield (%)	M.p. (°C)	Mol. Formula (Mol. Weight)
1	H	58	300	$C_9H_6N_4$ (170.17)
2		62	268	$C_{21}H_{14}N_4$ (322.37)
3		65	210	$C_{23}H_{18}N_4$ (350.42)
4		76	192	$C_{23}H_{18}N_4O_2$ (382.42)
5		72	180	$C_{21}H_{12}Cl_2N_4$ (391.26)
6		51	310	$C_{17}H_{10}N_4O_2$ (302.29)
7		78	214	$C_{17}H_{10}N_4S_2$ (334.41)
8		75	300	$C_{21}H_{12}N_4$ (330.43)

2:IR (KBr, cm^{-1}): 3360-2460 (N-H), 1650-1400 (C=N, C=C), 763, 696 (Monosubstituted benzene). **^{1}H-NMR** (DMSO-d_6) σ (ppm) :7.2-7.8 (10H, m, Ar-H), 8.45 (2H, s, $C_{4,9}$-H), 8.68 (1H, s, C_2-H).

3:IR (KBr, cm^{-1}): 3300-2300 (N-H), 1654-1442 (C=N, C=C). **^{1}H-NMR** (DMSO-d_6) σ (ppm) :2.47 (6H, s, Ar-CH_3), 7.26 (2H, d, j:7.69 Hz, Ar- $C_{3,5}$-H), 7.48 (2H, d, j:7.91 Hz, Ar-$C_{2,6}$-H), 8.66 (1H, s, C_2-H).

6:IR (KBr, cm^{-1}): 3350-2450 (N-H), 1635-1400 (C=N, C=C), 1250, 1060 (C-O). **^{1}H-NMR** (DMSO-d_6) σ (ppm) :6.68 (4H, s, furyl-$CH_{3,4}$-H), 7.89 (2H, s, furyl-CH_5-H), 8.13 (2H, s, $C_{4,9}$-H), 8.95 (1H, s, C_2-H).

8:IR (KBr, cm^{-1}): 3300-2450 (N-H), 1625-1417 (C=N, C=C). **^{1}H-NMR** (DMSO-d_6) σ (ppm) :7.85-8.05 (4H, m, $CH_{7,8,11,12}$-H), 8.59 (2H, s, $CH_{4,15}$-H), 8.75-8.95 (3H, m, C_2-H and $C_{6,13}$-H), 9.30-9.45 (2H, m, $C_{9,10}$-H).

Determination of the antibacterial and antifungal activities

Antibacterial ve antifungal activites of the compounds were determined using the tube dilution technique(7). The stock solutions of the compounds were prepared in DMSO. Chloramphenicole and Fluconazole were used as control antibactrial 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

Imidazo-quinoxaline derivatives were obtained reacting 4,5-diaminobenzimidazole with the suitable dicarbonyl compounds. The structure of the componds were elucidated with spectral methods and elemental analyses. In the IR spectra, the broad bands at 3150-2460 cm^{-1} due to N-H are very characteristic for imidazole or benzimidazole moiety(8).

In the NMR spectra, the signals due to C_2-H and $C_{4,9}$-H protons which are common in all compounds are observed as signlets at about 8.6 and 8.4 ppm respectively. The signals of other aromatic, methyl, methoxy protons were obtained as expected.

The most sensitive microorganism for the control for antibiotic chloramphenicole appeared to be *E.coli* and *C.albicans* for the control for antifungal fluconazole. By looking at the results we may conclude that our products have noticeable antibacterial and antifungal acvities. The

Table 2. Antibacterial and antifungal activities of the compounds

Comp.	E.C.	Ps.A.	C.A.	C.P.	T.G.
1	62.5	125	32.25	62.5	62.5
2	250	250	62.5	125	125
3	250	250	125	250	125
4	250	250	125	250	250
5	62.5	125	62.5	125	125
6	62.5	125	62.5	125	125
7	125	125	62.5	125	250
8	250	250	125	125	250
Chloramphenicole	0.9	15.6	31.25	62.5	31.25
Fluconazole	62.5	62.5	0.9	62.5	15.6

E.C. : *Echerichia coli*, Ps.A.: *Pseudomonas aeroginosa*, C.A.: *Candida albicans*, C.P.: *Candida parapsilosus*, T.G.: *Torulopsis globrata*

MIC values of chloramphenicole are 0.9 and 15.6 μg/ml against E.coli and P. aeroginosa respectively. Therefore some of our compounds which possess lower MIC values such as 62.5 μg/ml may be considered as notably potential antibacterial. The MIC values of fluconazole are 0.9, 62.5 and 15.6 μg/ml against C.albicans, C.parapsilosus and T.globrata, respectively. Hence our compounds may be regarded as highly active antifungals against these fungi.

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