INTRODUCTION

The treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including emerging infectious diseases and the increasing number of multi-drug resistant microbial pathogens. There is already evidence that antibacterial resistance is associated with an increase in mortality. Frequently, it is recommended to use new antibacterial agents with enhanced broad-spectrum potency. Therefore, recent efforts have been directed toward exploring novel antibacterial agents (1-4). Apart from this, the incidence of fungal infections in the immunocompromised population has significantly increased over the past two decades. Frequent infections caused by molds which may be primarily resistant to azoles and azole-resistant isolates of Candida species have increasingly been reported (5-7).

In drug designing programs an essential component of the search for new leads is the synthesis of molecules, which are novel yet resemble known biologically active molecules by virtue of the presence of critical structural features (8).

Carbazole and its derivatives are an important type of nitrogen containing aromatic heterocyclic compounds, possess desirable electronic and charge-transport properties, as well as large rπ-conjugated system, and the various functional groups are easily introduced into the structurally rigid carbazole ring (9). These characteristics result in the extensive potential applications of carbazole-based derivatives in the field of medicinal chemistry (antitumor, antimicrobial, antihistaminic, antioxidative, anti-inflammatory, psychotropic agents etc.) (10). Carbazole ring is present in a variety of naturally occurring medicinally active substances. For example, the carbazomycins are an unprecedented class of antibiotics with a carbazole framework (11,12). Carbazomycins A and B inhibit the growth of phytopathogenic fungi and have antibacterial and antifungal activities. However, Murrayafoline A exhibited strong fungicidal activity against Cladosporium cucumerinum which was isolated from Murraya euchrestifolia (13).

Electron-rich nitrogen heterocyclics play an important role in diverse biological activities (14, 15). Nitrogen heterocyclics particularly azole antifungal agents have gained great importance as therapeutic options for treatment of systemic fungal infections. The azoles that are available for
systemic use can be classified into two groups: the triazoles (fluconazole, itraconazole, voriconazole, posaconazole) and the imidazoles (ketoconazole) (16). The antimicrobial activities of imidazoles and benzimidazoles have long been established. Derivatives of these compounds are known for their antibacterial, trichomonacidal, anthelmintic, fungicidal, and antiviral activities. The success with these compounds stimulated the search for new biologically active derivatives (17).

On the other hand, sulfur and/or nitrogen heterocycles that possess pharmaceutical activities widely occur in nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cells. (18-20).

In the interest of the above suggestion, I planned to synthesize a system that combines together two biolabile components which are carbazole and nitrogen heterocyclics to give a compact structure like the title compounds.

**Chemistry**

The synthetic route of the compounds is outlined in Scheme 1. For the synthesis of the title compounds, 2-chloro-N-(9-ethyl-9H-carbazol-3-yl)acetamide required as starting material was prepared by the reaction of 3-amino-9-ethyl-9H-carbazole with chloroacetyl chloride (21). The reaction of equimolar quantities of 2-chloro-N-(9-ethyl-9H-carbazol-3-yl)acetamide with appropriate mercapto-heterocycles resulted in the formation of the title compounds (A1-9) (Table 1).

![Scheme 1. Synthetic protocol of the title compounds](image)

**Biology**

**Antimicrobial activity**

Antimicrobial activities of compounds were tested using microbroth dilution method (22,23). Tested microorganism strains were; Candida albicans (NRRL Y-27077), Candida albicans (isolate obtained from Faculty of Medicine, Osmangazi University), Candida glabrata (ATCC 36583), Escherichia coli (ATCC 10798), Staphylococcus aureus (ATCC 6538), Pseudomonas aeruginosa (ATCC 7700). Chloramphenicol and ketoconazole were used as control drugs. The observed data on the antimicrobial activity of the compounds and control drugs were given in Table 2.

![Table 2. MIC values of the compounds as μg/ml](image)

**EXPERIMENTAL**

**Chemistry**

All melting points (m.p.) were determined in open capillaries on a Gallenkamp apparatus and are uncorrected. The purity of the compounds was routinely checked by thin layer chromatography (TLC) using silica gel 60G (Merck). Spectroscopic data were recorded on the following instruments: IR, Shimadzu IR-435 spectrophotometer using KBr, 1H NMR, Bruker 500 MHz NMR spectrometer in DMSO-d$_6$ using TMS as an internal standard; FAB-MS VG Quattro mass spectrometer. Ele-

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**TABLE 1. Some characteristics of the compounds**

<table>
<thead>
<tr>
<th>Compounds</th>
<th>R</th>
<th>M. p. °C</th>
<th>Yield %</th>
<th>Mol. formula</th>
<th>M.W.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td></td>
<td>141-142</td>
<td>75</td>
<td>C$<em>{19}$H$</em>{19}$N$_3$O$_2$S</td>
<td>369</td>
</tr>
<tr>
<td>A2</td>
<td></td>
<td>113-115</td>
<td>82</td>
<td>C$<em>{18}$H$</em>{17}$N$_5$O$_2$S</td>
<td>383</td>
</tr>
<tr>
<td>A3</td>
<td></td>
<td>156-157</td>
<td>69</td>
<td>C$<em>{19}$H$</em>{19}$N$_5$O$_2$S</td>
<td>365</td>
</tr>
<tr>
<td>A4</td>
<td></td>
<td>200-201</td>
<td>67</td>
<td>C$<em>{19}$H$</em>{19}$N$_5$O$_2$S</td>
<td>366</td>
</tr>
<tr>
<td>A5</td>
<td></td>
<td>185-186</td>
<td>72</td>
<td>C$<em>{20}$H$</em>{20}$N$_4$O$_2$S</td>
<td>419</td>
</tr>
<tr>
<td>A6</td>
<td></td>
<td>150-152</td>
<td>79</td>
<td>C$<em>{20}$H$</em>{20}$N$_4$O$_2$S</td>
<td>417</td>
</tr>
<tr>
<td>A7</td>
<td></td>
<td>127-128</td>
<td>65</td>
<td>C$<em>{22}$H$</em>{22}$N$_4$O$_2$S</td>
<td>400</td>
</tr>
<tr>
<td>A8</td>
<td></td>
<td>202-204</td>
<td>68</td>
<td>C$<em>{22}$H$</em>{22}$N$_4$O$_2$S</td>
<td>401</td>
</tr>
<tr>
<td>A9</td>
<td></td>
<td>83-85</td>
<td>70</td>
<td>C$<em>{22}$H$</em>{22}$N$_4$O$_2$S</td>
<td>417</td>
</tr>
</tbody>
</table>
mental analyses were performed on a Perkin Elmer EAL 240 elemental analyzer.

Preparation of 2-chloro-N-(9-ethyl-9H-carbazol-3-yl)acetamide

Chloroacetyl chloride (0.1 mol) was added drop wise with stirring to a mixture 3-amino-9-ethyl-9H-carbazole (0.1mol) and triethylamine in toluene at 0-5 °C. The solvent was evaporated under reduced pressure. The residue was washed with water to remove triethylamine hydrochloride and crystallized from ethanol (21).

Preparation of 2-(Heterocyclic)sulfanyl-N-(9-ethyl-9H-carbazol-3-yl)acetamides A1-9

A mixture of 2-chloro-N-(9-ethyl-9H-carbazol-3-yl)acetamide (2 mmol) and appropriate mercapto-heterocyclics (2 mmol) in acetone was stirred at room temperature for 8 h in the presence of potassium carbonate. The residue was washed with water and crystallized from ethanol.

A1: 2-(4,5-Dihydro-thiazol-2-yl)sulfanyl-N-(9-ethyl-9H-carbazol-3-yl)acetamide

IR (KBr) max (cm-1): 3252 (amide N-H), 3061 (aromatic C-H), 1685 (amide C=O), 1582, 1490 (C=N and C=C), 1351, 1005 (C-N).

A2: 2-(5-Amino-[1,3,4]thiadiazol-2-yl)sulfanyl-N-(9-ethyl-9H-carbazol-3-yl)acetamide

IR (KBr) max (cm-1): 3252 (amide N-H), 3061 (aromatic C-H), 1685 (amide C=O), 1582, 1490 (C=N and C=C), 1351, 1005 (C-N).

A3: 2-(4-methyl-4H-[1,2,4]triazol-3-yl)sulfanyl-N-(9-ethyl-9H-carbazol-3-yl)acetamide

IR (KBr) max (cm-1): 3252 (amide N-H), 3061 (aromatic C-H), 1685 (amide C=O), 1582, 1490 (C=N and C=C), 1351, 1005 (C-N).

A4: 2-(1-phenyl-1H-tetrazol-5-yl)sulfanyl-N-(9-ethyl-9H-carbazol-3-yl)acetamide

IR (KBr) max (cm-1): 3252 (amide N-H), 3061 (aromatic C-H), 1685 (amide C=O), 1582, 1490 (C=N and C=C), 1351, 1005 (C-N).

A5: 2-(1-methyl-1H-tetrazol-5-yl)sulfanyl-N-(9-ethyl-9H-carbazol-3-yl)acetamide

IR (KBr) max (cm-1): 3252 (amide N-H), 3061 (aromatic C-H), 1685 (amide C=O), 1582, 1490 (C=N and C=C), 1351, 1005 (C-N).

A6: 2-(pyrimidin-2-yl)sulfanyl-N-(9-ethyl-9H-carbazol-3-yl)acetamide

IR (KBr) max (cm-1): 3252 (amide N-H), 3061 (aromatic C-H), 1685 (amide C=O), 1582, 1490 (C=N and C=C), 1351, 1005 (C-N).
Bazı yeni karbazol türevlerinin sentezleri ve antimikrobiyal aktivitelerinin araştırılması


ANAHTAR KELİMELER: Karbazol, antimikrobiyal aktive

A7: 2-(1H-Benzimidazol-2-yl)sulfanyl-N-(9-etil-9H-karbazol-3-il)acetamid
IR (KBr) max (cm⁻¹): 3299 (amide N-H ), 3101 (aromatic C-H), 1702 (amide C=O), 1588 1455 (C=N and C=C), 1301, 1198 (C=O), 1690 (amide C=O), 1612, 1505, 1410 (C=N and C=C), 1282, 1089 (C-N).

$$^{1}$$H-NMR (500 MHz, DMSO-d₆): 1.30 (3H, t, CH₃), 4.30 (2H, s, S-CH₂), 4.40-4.50 (2H, q, CH₂), 7.10-7.61 (9H, m, aromatic protons), 8.06 (1H, d (J= 7.74 Hz), carbazole-C₄), 8.43 (1H, s, carbazole-C₄), 10.03 (1H, s, NH), 12.70 (1H, s, benzimidazole NH). For C₂₃H₁₉N₄O₂S: calculated: C: 68.98%, H: 4.99%, N: 14.02%.

For C₂₃H₂₀N₄O₂S, calculated: C: 68.98%, H: 5.03%, N: 13.99%.

Mass spectra (FAB) [M+1]+: m/z 401

A8: 2-(Benzoxazol-2-yl)sulfanyl-N-(9-etil-9H-karbazol-3-il)acetamid
IR (KBr) max (cm⁻¹): 3280 (amide N-H ), 3111 (aromatic C-H), 1690 (amide C=O), 1612, 1505, 1410 (C=N and C=C), 1282, 1089 (C-N).

$$^{1}$$H-NMR (500 MHz, DMSO-d₆): 1.33 (3H, t, CH₃), 4.30 (2H, s, S-CH₂), 4.35-4.44 (2H, q, CH₂), 6.90-7.74 (9H, m, aromatic protons), 8.06 (1H, d (J= 7.80 Hz), carbazole-C₂), 8.43 (1H, s, carbazole-C₄), 10.03 (1H, s, NH), 12.70 (1H, s, benzimidazole NH).

For C₂₃H₁₉N₄O₂S: calculated: C: 68.85%, H: 4.80%, N: 10.51%.

For C₂₃H₂₀N₄O₂S, calculated: C: 68.81%, H: 4.77%, N: 10.47%.

Mass spectra (FAB) [M+1]+: m/z 402

A9: 2-(Benzothiazol-2-yl)sulfanyl-N-(9-etil-9H-karbazol-3-il)acetamid
IR (KBr) max (cm⁻¹): 3261 (amide N-H ), 3088 (aromatic C-H), 1695 (amide C=O), 1602, 1536, 1422 (C=N and C=C), 1298, 1068 (C-N).

$$^{1}$$H-NMR (500 MHz, DMSO-d₆): 1.35 (3H, t, CH₃), 4.40-4.44 (2H, q, CH₂), 4.46 (2H, s, S-CH₂), 7.18 (1H, t (J= 7.31 and 7.67 Hz), carbazole-C₄), 7.36-7.61 (6H, m, aromatic protons), 7.86-8.09 (3H, m, aromatic protons), 8.43 (1H, s, carbazole-C₄), 10.03 (1H, s, NH).

For C₂₃H₁₉N₄O₂S: calculated: C: 66.20%, H: 4.58%, N: 10.05%.

Mass spectra (FAB) [M+1]+: m/z 418

**Biology**

Antimicrobial activity

Microdilution broth susceptibility assay was used for the antibacterial evaluation of the compounds (22), whereas antifungal susceptibility of the yeasts were examined according to NCCLS reference method for broth dilution antifungal susceptibility testing of yeasts (23). Chloramphenicol was used as standard antibacterial agent and ketoconazole was used as antifungal agent. And both are prepared as described in the related references.

**RESULTS AND DISCUSSION**

In the present work, 9 new compounds (A1-9) were synthesized. The structures of the obtained compounds were elucidated by spectral data. According to the IR spectroscopic data of the compounds, NH stretching bands were observed in 3225-3299 cm⁻¹ region. The compounds showed characteristic C=O (amide) stretching bands in 1702-1682 cm⁻¹ region. In the $^{1}$$H$-NMR spectra of the compounds, NH peaks were observed at 10.03-10.05 ppm region. The signal due to COCH₂ methylene protons, presented in all compounds, appeared at 4.05–4.50 ppm, as singlets. While the CH₂ protons of ethyl group were observed at 4.35-4.55 ppm as quartets, the CH₃ protons of ethyl group were observed at 1.27-1.35 ppm as triplets. All the other aromatic and aliphatic protons were observed at expected regions.

Mass spectra (FAB) of compounds showed a M+1 peaks, in agreement with their molecular formula.

The most important part of the results was those which are obtained from antifungal activity screening. Most of the compounds were effective against C. albicans (NRRLY-27077). When compared with ketoconazole; especially A3, A4 showed similar activity, and A1, A2, A5, A6 exhibited moderate activity against C. albicans (NRRLY-27077). Similar results were obtained from C. glabrata. Compound A3 showed similar activity and A1, A2, A4, A5 and A6 exhibited moderate activity against C. glabrata when compared with ketoconazole. By comparing their MIC values with ketoconazole, compounds A3, A4, A5 were moderate active against C. albicans (clinical isolate).

The result of antibacterial screening of newly prepared compounds expressed as the MIC is summarized in Table 2. The antibacterial assessment revealed that the compounds possess only a moderate or slight activity. The MIC values are gener-
ally within the range of 100 - >400 μg/ml against all evaluated strains. By comparing their MIC values with chloramphenicol, the compounds were less active against E. coli and S. aureus. On the other hand the compounds exhibited comparable or better activities against P. aeruginosa then those of chloramphenicol.

ACKNOWLEDGEMENTS
The author would like to thank Anadolu Üniversitesi Bitki, İlaç ve Bilimsel Araştırmalar Merkezi (AÜBİBAM) for spectroscopic analyses and biological activity tests.

REFERENCES