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ORIGINAL RESEARCH

Synthesis of some novel Carbazole derivatives and evaluation of their antimicrobial activity

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ABSTRACT: Carbazole and its derivatives are an important type of nitrogen containing aromatic heterocyclic compounds which have attracted considerable attention of medicinal chemists due to their antimicrobial activities. For this purpose, new carbazole derivatives were synthesized and evaluated for antimicrobial activity. As starting material 2-chloro-N-(9-ethyl-9H-carbazol-3-yl)acetamide was prepared by the reaction of 3-amino-9-ethyl-9H-carbazole with chloroacetyl chloride. The reaction of 2-chloro-N-(9-ethyl-9H-carbazol-3-yl)acetamide with appropriate mercapto-heterocyclics resulted in the formation of the title compounds. The chemical structures of the compounds were elucidated by IR, 1H-NMR, FAB-MS spectral data and elemental analysis. Their antimicrobial activities against *Candida albicans* (two strains), *Candida glabrata*, *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa* were investigated.

KEY WORDS: Carbazole, antimicrobial activity

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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 π-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 antiyeast 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)

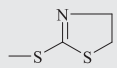
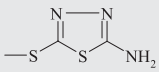
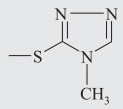
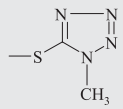
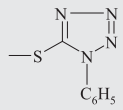
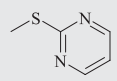
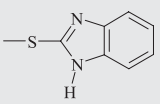
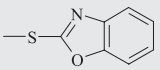
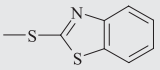
On the other hand, sulfur and/or nitrogen heterocycles that possess pharmaceutical activities widely occur in nature in the form of alkaloids, vitamins, pigments and as constituents of plant and animal cells. (18-20).

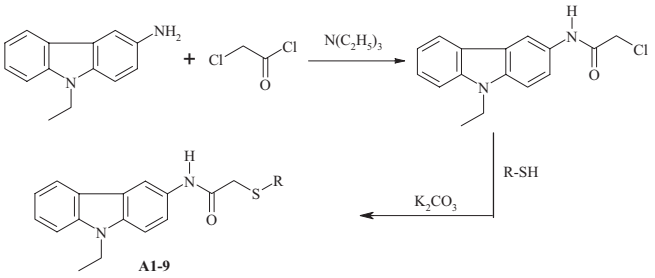
In the interest of the above suggestion, I planned to synthesize a system that combines together two biolabile components which are carbazole and nitrogen heterocyclics to give a compact structure like the title compounds.

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-heterocyclics resulted in the formation of the title compounds (**A1-9**) (Table 1).

TABLE 1. Some characteristics of the compounds

Compounds	R	M.p. (°C)	Yield %	Mol. formula	M.W.
A1		141-142	75	$C_{19}H_{19}N_3OS_2$	369
A2		113-115	82	$C_{18}H_{17}N_5OS_2$	383
A3		156-157	69	$C_{19}H_{19}N_5OS$	365
A4		200-202	67	$C_{18}H_{18}N_6OS$	366
A5		185-186	72	$C_{23}H_{20}N_6OS$	428
A6		150-152	79	$C_{20}H_{18}N_4OS$	362
A7		127-128	65	$C_{23}H_{20}N_4OS$	400
A8		202-204	68	$C_{23}H_{19}N_3O_2S$	401
A9		83-85	70	$C_{23}H_{19}N_3OS_2$	417



SCHEME 1. Synthetic protocol of the title compounds

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

Compounds	A	B	C	D	E	F
A1	8	>16	16	100	200	200
A2	8	>16	16	100	200	200
A3	4	16	8	100	200	200
A4	4	16	16	100	200	400
A5	8	16	16	100	400	400
A6	8	>16	16	200	400	>400
A7	16	>16	>16	200	>400	>400
A8	>16	>16	>16	200	>400	>400
A9	>16	>16	>16	200	400	>400
Ketoconazole	4	8	8	-	-	-
Chloramphenicol	-	-	-	25	12.5	100

A: *C. albicans* (NRRL Y-27077), B: *C. albicans* (isolate obtained from Faculty of Medicine, Osmangazi University), C: *C. glabrata* (ATCC 36583), D: *E. coli* (ATCC 10798), E: *S. aureus* (ATCC 6538), F: *P. aeruginosa* (ATCC 7700).

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, ^{1}H NMR, Bruker 500 MHz NMR spectrometer in DMSO-d_6 using TMS as an internal standard; FAB-MS VG Quattro mass spectrometer. Ele-

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}): 3225 (amide N-H), 3051 (aromatic C-H), 1685 (amide C=O), 1605 1540, 1432 (C=N and C=C), 1341, 1011 (C-N).

^{1}H-NMR (500 MHz, DMSO-d_6): 1.30 (3H, t, CH_3), 3.50 (2H, t, thiazoline-C_4), 4.12 (2H, s, S-CH_2), 4.17 (2H, t, thiazoline-C_5), 4.40-4.46 (2H, q, CH_2), 7.19 (1H, t(J= 7.52 and 7.33 Hz), carbazole-C_6), 7.45 (1H, t (J= 7.85 and 7.47 Hz), carbazole-C_7), 7.52-7.61 (3H, m, C_1,C_5,C_8 protons of carbazole), 8.07 (1H, d (J= 7.67 Hz), carbazole-C_2), 8.41 (1H, s, carbazole-C_4), 10.03 (1H, s, NH).

For $C_{19}H_{19}N_3OS_2$, calculated: C: 61.76%; H: 5.18%; N: 11.37%; found: C: 61.72%; H: 5.21%; N: 11.40 %.

MS (FAB) $[M+1]^+$: m/z 370

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

IR (KBr) max (cm^{-1}): 3276 (amide N-H), 3092 (aromatic C-H), 1682 (amide C=O), 1620, 1525, 1442 (C=N and C=C), 1351, 1005 (C-N).

^{1}H-NMR (500 MHz, DMSO-d_6): 1.32 (3H, t, CH_3), 4.05 (2H, s, S-CH_2), 4.40-4.50 (2H, q, CH_2), 7.19 (1H, t(J= 7.49 and 7.37 Hz), carbazole-C_6), 7.33 (2H, s, NH_2), 7.45 (1H, t (J= 7.64 and 7.48 Hz), carbazole-C_7), 7.53-7.62 (3H, m, C_1,C_5,C_8 protons of carbazole), 8.08 (1H, d (J= 7.72 Hz), carbazole-C_2), 8.41 (1H, s, carbazole-C_4), 10.03 (1H, s, NH).

For $C_{18}H_{17}N_5OS_2$, calculated: C: 56.38%, H: 4.47%, N: 18.26%, found: C: 56.41%, H: 4.50%, N: 18.25%.

MS (FAB) $[M+1]^+$: m/z 384

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}): 3260 (amide N-H), 3092 (aromatic C-H), 1683 (amide C=O), 1539 1421 (C=N and C=C), 1288, 1051 (C-N).

^{1}H-NMR (500 MHz, DMSO-d_6): 1.27 (3H, t, CH_3), 3.65 (3H, s, triazole-CH_3), 4.10 (2H, s, S-CH_2), 4.40-4.55 (2H, q, CH_2), 7.19(1H, t(J= 7.47 and 7.39 Hz), carbazole-C_6), 7.45 (1H, t (J= 7.35 and 7.94 Hz), carbazole-C_7), 7.50-7.62 (3H, m, C_1,C_5,C_8 protons of carbazole), 8.07 (1H, d (J= 7.77 Hz), carbazole-C_2), 8.38 (1H, s, carbazole-C_4), 8.59 (1H, s, triazole-C_5), 10.03 (1H, s, NH).

For $C_{19}H_{19}N_5OS$, calculated: C: 62.45%, H: 5.24%, N: 19.16%, found: C: 62.47%, H: 5.28%, N: 19.12%,

MS (FAB) $[M+1]^+$: m/z 366

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

IR (KBr) max (cm^{-1}): 3271 (amide N-H), 3096 (aromatic C-H), 1692 (amide C=O), 1588, 1512, 1430 (C=N and C=C), 1296, 1068 (C-N).

^{1}H-NMR (500 MHz, DMSO-d_6): 1.32 (3H, t, CH_3), 4.05 (3H, s, tetrazole-CH_3), 4.35 (2H, s, S-CH_2), 4.40-4.50 (2H, q, CH_2), 7.19 (1H, t(J= 7.53 and 7.38 Hz), carbazole-C_6), 7.43-7.48 (1H, m, carbazole-C_7), 7.52-7.61 (3H, m, C_1,C_5,C_8 protons of carbazole), 8.08 (1H, d (J= 7.68 Hz), carbazole-C_2), 8.39 (1H, s, carbazole-C_4), 10.04 (1H, s, NH).

For $C_{18}H_{18}N_6OS$ calculated: C: 59.00%, H: 4.95%, N:22.93% , found: C: 59.02%, H: 4.97%, N:22.96%

MS (FAB) $[M+1]^+$: m/z 367

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

IR (KBr) max (cm^{-1}): 3238 (amide N-H), 3126 (aromatic C-H), 1699 (amide C=O), 1625, 1552, 1436 (C=N and C=C), 1301, 1099 (C-N).

^{1}H-NMR (500 MHz, DMSO-d_6): 1.33 (3H, t, CH_3), 4.40-4.45 (2H, q, CH_2), 4.50 (2H, s, S-CH_2), 7.18 (1H, t(J= 7.51 and 7.33 Hz), carbazole-C_6), 7.45 (1H, t(J= 7.67 and 7.60 Hz), carbazole-C_7), 7.53-7.76 (8H, m, aromatic protons), 8.07 (1H, d (J= 7.76 Hz), carbazole-C_2), 8.40 (1H, s, carbazole-C_4), 10.05 (1H, s, NH).

For $C_{23}H_{20}N_6OS$ calculated: C: 64.47%, H: 4.70%, N: 19.61%, found: C: 64.49%, H: 4.74%, N: 19.64%,

MS (FAB) $[M+1]^+$: m/z 429

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), 1679 (amide C=O), 1592 1522, 1401 (C=N and C=C), 1311, 1011 (C-N).

^{1}H-NMR (500 MHz, DMSO-d_6): 1.33 (3H, t, CH_3), 4.15 (2H, s, S-CH_2), 4.45-4.50 (2H, q, CH_2), 7.18 (1H, t(J=7.39 and 7.46 Hz), carbazole-C_6), 7.24-7.28 (1H, m, pyrimidine-C_5), 7.46 (1H, t (J= 7.31 and 7.97 Hz), carbazole-C_7), 7.50-7.61 (3H, m, C_1,C_5,C_8 protons of carbazole), 8.06 (1H, d (J= 7.76 Hz), carbazole-C_2), 8.42 (1H, s, carbazole-C_4), 8.66-8.69 (2H, dd (J=1.21 and 1.17 Hz), C_4 and C_6 protons of pyrimidine), 10.03 (1H, s, NH).

For $C_{20}H_{18}N_4OS$, calculated: C: 66.28%, H: 5.01%, N: 15.46, found: C: 66.32%, H: 5.06%, N: 15.51%.

MS (FAB) $[M+1]^+$: m/z 363

Bazı yeni karbazol türevlerinin sentezleri ve antimikrobiyal aktivitelerinin araştılılması

ÖZET: Karbazol ve türevleri, antimikrobiyal aktiviteleri nedeniyle medisinal kimyacıların ilgisini çeken azotlu heterosiklik bileşiklerdir. Bu amaçla yeni karbazol türevleri sentezlendi ve antimikrobiyal aktiviteleri araştırıldı. Başlangıç maddesi olarak 2-kloro-N-(9-etil-9H-karbazol-3-il)asetamid, 3-amino-9-etil-9H-karbazol ile kloroasetil klorürün reaksiyonuyla hazırlandı. 2-Kloro-N-(9-etil-9H-karbazol-3-il)asetamid ile merkapto-heterosikliklerin reaksiyonu ile sonuç bileşikleri elde edildi. Bileşiklerin kimyasal yapıları IR, 1H-NMR, FAB-MS spektroskopik verileri ve elemental analiz ile aydınlatıldı. Bileşiklerin antimikrobiyal aktiviteleri *Candida albicans* (iki suş), *Candida glabrata*, *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*'a karşı araştırıldı.

ANAHTAR KELİMELER: Karbazol, antimikrobiyal aktivite

A7: 2-(1H-Benzoimidazol-2-yl)sulfanyl-N-(9-ethyl-9H-carbazol-3-yl)acetamide

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-N).

^{1}H-NMR (500 MHz, DMSO-d_6): 1.30 (3H, t, CH_3), 4.30 (2H, s, S-CH_2), 4.40-4.50 (2H, q, CH_2), 7.10-7.61 (9H, m, aromatic protons), 8.06 (1H, d (J= 7.74 Hz), carbazole-C_2), 8.43 (1H, s, carbazole-C_4), 10.04 (1H, s, NH), 12.70 (1H, s, benzimidazole NH).

For $C_{23}H_{20}N_4OS$, calculated: C: 68.98%, H: 5.03%, N: 13.99%, found: C: 68.95%, H: 4.99%, N: 14.02%.

MS (FAB) $[M+1]^+$: m/z 401

A8: 2-(Benzoxazol-2-yl)sulfanyl-N-(9-ethyl-9H-carbazol-3-yl)acetamide

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-d_6): 1.33 (3H, t, CH_3), 4.30 (2H, s, S-CH_2), 4.35-4.45 (2H, q, CH_2), 6.90-7.74 (9H, m, aromatic protons), 8.06 (1H, d (J= 7.80 Hz), carbazole-C_2), 8.43 (1H, s, carbazole-C_4), 10.05 (1H, s, NH).

For $C_{23}H_{19}N_3O_2S$, calculated: C: 68.81%, H: 4.77%, N: 10.47%, found: C: 68.85%, H: 4.80%, N: 10.51%.

MS (FAB) $[M+1]^+$: m/z 402

A9: 2-(Benzothiazol-2-yl)sulfanyl-N-(9-ethyl-9H-carbazol-3-yl)acetamide

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-d_6): 1.35 (3H, t, CH_3), 4.40-4.44 (2H, q, CH_2), 4.46 (2H, s, S-CH_2), 7.18 (1H, t (J= 7.31 and 7.67 Hz), carbazole-C_6), 7.36-7.61 (6H, m, aromatic protons), 7.86-8.09 (3H, m, aromatic protons), 8.43 (1H, s, carbazole-C_4), 10.05 (1H, s, NH).

For $C_{23}H_{19}N_3OS_2$ calculated: C: 66.16%, H: 4.59%, N: 10.06%, found: C: 66.20%, H: 4.58%, N: 10.05%.

MS (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 as singlets at about 10.03-10.05 ppm region. The signal due to $COCH_2$ methylene protons, presented in all compounds, appeared at 4.05–4.50 ppm, as singlets. While the CH_2 protons of ethyl group were observed at 4.35-4.55 ppm as quartets, the CH_3 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.

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