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ORIGINAL ARTICLE

Synthesis and antimicrobial activities of 9*H*-carbazole derivatives

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Abstract In this work 9*H*-carbazole was utilized as a precursor to prepare new heterocyclic derivatives. Treatment of carbazole **1** with ethyl acetoacetate gave ethyl 9*H*-carbazol-9-ylacetate **2**. The acetate ester derivative **2** was transformed into the 2-(9*H*-carbazol-9-yl)acetohydrazide **3** through treatment with hydrazine hydrate. Reaction of compound **3** with sodium nitrite/HCl afforded [(9*H*-carbazol-9-ylacetyl)amino]diazonium chloride **4**. Compounds 3-[3-(9*H*-carbazol-9-ylacetyl)triazanylidene]pentane-2,4-dione **5** and ethyl 2-[3-(9*H*-carbazol-9-ylacetyl)triazanylidene]-3-oxobutnoate **6** were obtained by reaction of compound **4** with acetylacetone and ethyl acetoacetate, respectively. Treatment of compounds **5** and **6** with urea and phenylhydrazine afforded 5-[3-(9*H*-carbazol-9-ylacetyl)triazanylidene]-4,6-dimethyl pyrimidin-2(5*H*)-one **7** and 4-[3-(9*H*-carbazol-9-yl acetyl)triazanylidene]-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one **8**, respectively. The structures of the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. All synthesized products were tested and evaluated as antimicrobial agents.

1. Introduction

Microorganisms cause different kinds of diseases to humans and animals. Discovery of chemotherapeutic agents played a very important role in controlling and preventing such diseases. Chemotherapeutic agents are isolated either from living organisms known as antibiotic like penicillin and tetracycline or they are chemical compounds prepared by chemists such as sulfa drugs (Rajakumar et al., 2008; Menor-Salván et al., 2009). Microorganisms have the ability to develop resistance to these chemotherapeutic agents and such strains which are resistance cause major problems in the treatment of microbial infections (Salimon et al., 2010a). For this reason, searching for new antimicrobial agent is continuous process and great efforts have been employed to find new antibiotic or new chemical compounds with good antimicrobial activity which might be suitable to be used as chemotherapeutic agents (Moellering et al., 2007; Rajakumar et al., 2009).

Carbazole and its derivatives are an important type of nitrogen containing aromatic heterocyclic compounds, possess desirable electronic and charge-transport properties, as well as

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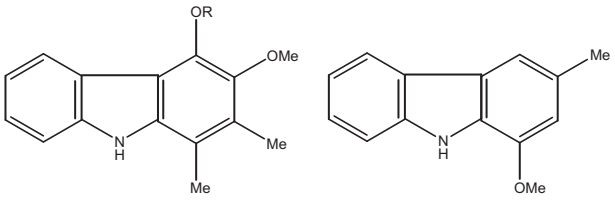

Figure 1 Structures of some biologically active carbazole compounds.

large π-conjugated system, the various functional groups are easily introduced into the structurally rigid carbazolyl ring. These characteristics result in the extensive potential applications of carbazole-based derivatives in the field of photoelectrical materials (Morin et al., 2005), dyes (Kim et al., 2007), supramolecular recognition (Zhou et al., 2009) and medicinal chemistry (antitumor, antimicrobial, antihistaminic, antioxidative, anti-inflammatory, psychotropic agents, etc.) (Knölker and Reddy, 2002; Mi et al., 2007; Cai et al., 2009; Bai et al., 2007). Carbazole ring is present in a variety of naturally occurring medicinally active substances (Knölker and Reddy, 2002). For example, the Carbazomycins are an unprecedented class of antibiotics with a carbazole framework (Knölker et al., 2003; Hagiwara et al., 2000), Carbazomycins A and B (Fig. 1) inhibit the growth of phytopathogenic fungi and have antibacterial and anti-yeast activities and Murrayafoline A, which was isolated from *Murraya euchrestifolia* Hayata collected in Taiwan (Cuong et al., 2008), exhibited strong fungicidal activity against *Cladosporium cucumerinum* at the dose of 12.5 μg.

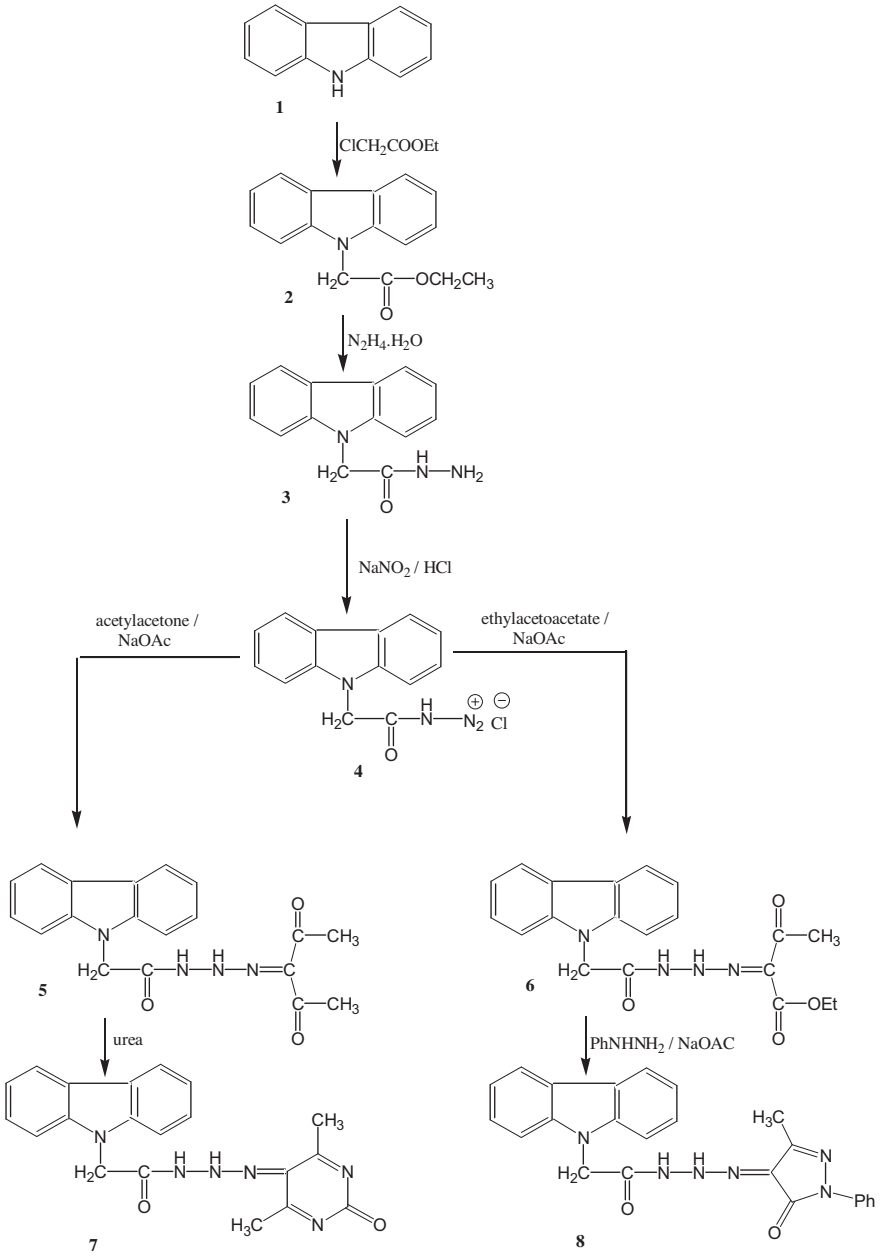

Figure 2 Synthetic protcol to synthesis compounds (**2**–**8**).

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In view of the above mentioned findings and as continuation of our efforts to identify new candidates that may be of value in designing new antimicrobial agents (Salimon et al., 2010b; Salimon and Salih, 2010a). We report here the synthesis of some carbazole-based azole derivatives in order to investigate their antimicrobial activity (Fig. 2).

2. Experimental

2.1. Measurements

Melting points were determined in open glass capillary tube on a Gallen-Kamp MFB-595 apparatus (United Kingdom) and are uncorrected. The IR spectra were taken on a Perkin-Elmer FT-IR 1650 (United States), using samples in KBr disks. The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on JEOL JNM-ECP 400 spectrometer (Japan) using DMSO-d_6 as solvent and TMS as the internal standard, the chemical shifts are expressed in δ_{ppm}. Elemental microanalysis was performed on a Perkin Elmer CHN-2400 analyzer (United States). All reactions were followed by TLC (Silica gel, aluminum sheets 60 F_{254}, Merck).

2.2. Synthesis

2.2.1. Ethyl 9H-carbazol-9-ylacetate 2

To a stirred solution of carbazole **1** (0.02 mol) in ethanol (25 mL), ethyl chloroacetate (0.02 mol) was added drop wise and the mixture was left stirred at room temperature overnight then the reaction mixture was poured into ice water (100 mL). The crude product was filtered off, washed with water and recrystalized from ethanol to give compound **2** as colorless needles. Yield: 81%; m.p. 80–81 °C; IR (KBr, cm^{-1}): 3090 (C–H stretching of aromatic ring), 2987 and 2865 (C–H streching of aliphatic group), 1745 (C═O stretching), 1046 (C–O–C stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 8.05 (1H, *d*, *J* = 8.23, Ar-H), 8.01 (1H, *d*, *J* = 16.04, Ar-H), 7.65 (1H, *d*, *J* = 8.25, Ar-H), 7.54 (1H, *d*, *J* = 16.10, Ar-H), 7.43 (1H, *t*, *J* = 7.98, Ar-H), 7.37 (1H, *t*, *J* = 8.15, Ar-H), 7.26 (1H, *t*, *J* = 7.95, Ar-H), 7.18 (1H, *t*, *J* = 8.11, Ar-H), 3.96 (2H, *q*, *J* = 8.65, CH_2CH_3), 3.76 (2H, *s*, CH_2), 2.10 (3H, *t*, *J* = 12.12, CH_2CH_3); ^{13}C NMR (100 MHz-DMSO-d_6, δ/ppm): 169.32, 137.25, 137.09, 136.85, 136.03, 135.90, 135.14, 134.60, 133.79, 133.05, 132.11, 131.27, 130.98, 13.15, 12.99, 10.52; Anal. Calcd. for $C_{16}H_{15}NO_2$ (253.11 g/mol): C, 75.87; H, 5.97; N, 5.53. Found: C, 75.88; H, 5.96; N, 5.52.

2.2.2. 2-(9H-Carbazol-9-yl)acetohydrazide 3

To a solution of the acetate ester **2** (0.01 mol) in absolute ethanol (25 mL), hydrazine hydrate 98% (0.021 mol) was added and the reaction mixture was heated under reflux for 4 h. Then reaction mixture was left stirring overnight. The separated solid product was filtered, dried and recrystalized from ethanol/H_2O (2:2) to yield compound **3** as a white crystals. Yield: 73%; m.p. 130–131 °C; IR (KBr, cm^{-1}): 3045 (C–H stretching of aromatic ring), 3330, 3274 ($NHNH_2$ stretching), 1645 (C═O stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 8.84 (2H, *s*, NH_2, D_2O exchangeable), 8.21 (1H, *s*, NH, D_2O exchangeable), 8.12 (1H, *d*, *J* = 11.89, Ar-H), 7.95 (1H, *d*, *J* = 7.88, Ar-H), 7.54 (1H, *d*, *J* = 7.96, Ar-H), 7.52 (1H, *d*, *J* = 12.08, Ar-H), 7.24 (1H, *t*, *J* = 11.79, Ar-H), 7.16 (1H, *t*, *J* = 12.69, Ar-H), 7.05 (1H, *t*, *J* = 7.78, Ar-H), 6.91 (1H, *t*, *J* = 8.09, Ar-H), 3.73 (2H, *s*, CH_2); ^{13}C NMR (100 MHz-DMSO-d_6, δ/ppm): 171.45, 137.14, 136.95, 136.70, 136.34, 135.87, 135.56, 135.21, 134.71, 133.10, 132.89, 132.34, 131.23, 10.66; Anal. Calcd. for $C_{14}H_{13}N_3O$ (255.27 g/mol): C, 65.87; H, 5.13; N, 16.46. Found: C, 65.86; H, 5.14; N, 16.45.

2.2.3. 3-[3-(9H-Carbazol-9-ylacetyl)triazanylidene]pentane-2,4-dione 5

A mixture of the diazonium salt **4** (0.01 mol), sodium acetate (0.01 mol) and acetylacetone (0.01 mol) in ethanol (25 mL) was stirring together in ice bath for 12 h. Then, the reaction mixture was poured into crushed ice and the solid deposits was filtered and recrystalized from ethanol/H_2O (2:2) to give the desired product **5**. Yield: 60%; m.p. 191–192 °C; N, 12.55; IR (KBr, cm^{-1}): 3234 (N–H stretching), 3056 (C–H stretching of aromatic ring), 2930, 2867 (C–H stretching of aliphatic group), 1702, 1645 (C═O stretching), 1620 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 8.23, 8.19 (2H, 2*s*, 2NH, D_2O exchangeable), 8.10 (1H, *d*, *J* = 11.90, Ar-H), 7.98 (1H, *d*, *J* = 7.79, Ar-H), 7.85 (1H, *d*, *J* = 11.59, Ar-H), 7.72 (1H, *d*, 15.69, Ar-H), 7.65 (1H, *t*, *J* = 12.11, Ar-H), 7.55 (1H, *t*, *J* = 11.67, Ar-H), 7.46 (1H, *t*, *J* = 11.79, Ar-H), 7.38 (1H, *t*, *J* = 12.20, Ar-H), 3.75 (2H, *s*, CH_2), 2.37, 2.34 (6H, 2*s*, $2CH_3$); ^{13}C NMR (100 MHz-DMSO-d_6, δ/ppm): 173.84, 171.69, 170.35, 137.66, 137.52, 136.39, 136.12, 135.68, 134.78, 133.65, 133.13, 132.50, 131.90, 130.41, 13.25, 13.02, 12.65, 9.98; Anal. Calcd. for $C_{19}H_{18}N_4O_4$ (366.37 g/mol): C, 62.29; H, 4.95; N, 15.29. Found C, 62.30; H, 4.94; N, 15.28.

2.2.4. Ethyl 2-[3-(9H-carbazol-9-ylacetyl)triazanylidene]-3-oxobutnoate 6

The same method described for the synthesis of compound **5** but using ethyl acetoacetate (0.01 mol) instead of acetyl acetone. Yield: 52%; m.p. 111-113 °C; IR (KBr, cm^{-1}): 3321 (N–H stretching), 3089 (C–H stretching of aromatic ring), 2924, 2831 (C–H stretching of aliphatic group), 1735, 1718, 1640 (C═O stretching), 1622 (C═N stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 8.24, 8.20 (2NH, 2*s*, 2H, D_2O exchangeable), 8.08 (1H, *d*, *J* = 8.39, Ar-H), 7.97 (1H, *d*, *J* = 7.92, Ar-H), 7.88 (1H, *d*, *J* = 8.09, Ar-H), 7.80 (1H, *d*, *J* = 7.57, Ar-H), 7.71 (1H, *t*, *J* = 7.68, Ar-H), 7.57 (1H, *t*, *J* = 7.75, Ar-H), 7.50 (1H, *t*, *J* = 7.81, Ar-H), 7.43 (1H, *t*, *J* = , 7.89, Ar-H), 3.93 (2H, *q*, *J* = 7.49, CH_2CH_3), 3.73 (2H, *s*, CH_2), 2.12 (3H, *t*, *J* = 7.90, CH_2CH_3), 1.98 (3H, *s*, CH_3); ^{13}C NMR (100 MHz-DMSO-d_6, δ/ppm): 173.34, 172.65, 171.90, 138.43, 138.15, 138.03, 137.51, 137.22, 136.81, 135.10, 134.76, 133.94, 133.06, 132.38, 131.09, 18.34, 13.94, 13.61, 12.38; Anal. Calcd. for $C_{20}H_{20}N_4O_5$ (396.40 g/mol): C, 60.60; H, 5.09; N, 14.13. Found: C, 60.59; H, 5.10; N, 14.12.

2.2.5. 5-[3-(9H-Carbazol-9-ylacetyl)triazanylidene]-4,6-dimethylpyrimidin-2(5H)-one 7

To a solution of compound **6** (0.01 mol) in ethanol (20 mL), urea (0.01 mol) was added and the reaction mixture was refluxed for 6 h. The reaction mixture was concentrated to approximately half of its volume and allowed to cool to room temperature. The solid product was filtered using suction pump, washed with thoroughly with water, dried and recrystalized from ethanol (Menor-Salván et al., 2009). Yield: 60%; m.p. 152–153 °C; IR (KBr, cm^{-1}): 3225 (N–H

stretching), 3090 (C–H stretching of aromatic ring), 2931, 2840 (C–H stretching of aliphatic group), 1645 (C=O stretching), 1624 (C=N stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 8.40, 8.38 (2NH, 2*s*, 2H , D_2O exchangeable), 8.10 (1H, *d*, *J* = 8.11, Ar-H), 7.96 (1H, *d*, *J* = 7.79, Ar-H), 7.85 (1H, *d*, *J* = 7.92, Ar-H), 7.78 (1H, *d*, *J* = 8.15, Ar-H), 7.69 (1H, *t*, *J* = 7.78, Ar-H), 7.55 (1H, *t*, *J* = 7.71, Ar-H), 7.46 (1H, *t*, *J* = 7.76, Ar-H), 7.41 (1H, t, *J* = 7.77, Ar-H), 3.17 (2H, *s*, CH_2), 2.49, 2.239 (6H, 2*s*, $2CH_3$); ^{13}C NMR (100 MHz-DMSO-d_6, δ/ppm): 172.31, 170.89, 138.57, 138.31, 137.58, 137.44, 136.02, 135.23, 135.14, 134.84, 134.46, 134.06, 133.18, 132.35, 18.15, 13.09, 13.03, 12.98; Anal. Calcd. for $C_{20}H_{18}N_6O_3$ (390.40 g/mol): C, 61.53; H, 4.65; N, 21.53. Found: C, 61.52; H, 4.66; N, 21.52.

2.2.6. 4-[3-(9H-Carbazol-9-yl acetyl)triazanylidene]-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one ***8***

A mixture of compound **6** (0.01 mol), anhydrous sodium acetate (0.01 mmol) and phenylhydrazine (0.01 mol) in ethanol (25 mL) was heated under reflux for 24 h. The reaction mixture was concentrated, diluted with water and stored in a refrigerator. The separated solid was filtered, washed with ether, dried and recrystalized from ethanol. Yield: 70%; m.p. 230–231 °C; IR (KBr, cm^{-1}): 3313 (N–H stretching), 3026 (C–H stretching of aromatic ring), 2924, 2836 (C–H stretching of aliphatic group), 1642 (C=O stretching), 1622 (C=N stretching); ^{1}H NMR (400 MHz, DMSO-d_6, δ/ppm): 8.54, 8.31 (2NH, 2*s*, 2H , D_2O exchangeable), 8.05 (1H, *d*, *J* = 7.95, Ar-H), 7.94 (1H, *d*, *J* = 8.17, Ar-H), 7.80 (1H, *d*, *J* = 8.12, Ar-H), 7.75 (2H, *m*, *J* = 8.54, Ar-H), 7.60 (1H, *t*, *J* = 7.85, Ar-H), 7.56 (2H, *m*, *J* = 8.67, Ar-H), 7.45 (1H, *t*, *J* = 8.23, Ar-H), 7.39 (2H, *m*, *H* = 7.92, Ar-H), 7.30 (2H, *m*, *J* = 8.58, Ar-H), 3.15 (2H, *s*, CH_2), 2.90 (3H, *s*, CH_3); ^{13}C NMR (100 MHz-DMSO-d_6, δ/ppm): 173.31, 172.40, 140.78, 140.66, 140.27, 139.40, 138.90, 138.42, 138.12, 137.62, 137.23, 137.11, 136.83, 136.50, 136.32, 135.71, 134.62, 133.60, 133.05, 132.12, 131.51, 12.75, 12.10, 11.98, 10.03; Anal. Calcd. for $C_{24}H_{20}N_6O_3$ (440.45 g/mol): C, 65.45; H, 4.58; N, 19.08. Found: C, 65.46; H, 4.59; N, 19.09.

3. Results and discussion

3.1. Chemistry

The synthetic procedure adopted to obtain the target compounds are outlined in Fig. 2. Reaction of compound **1** with ethyl chloroacetate in ethanol, leading to ethyl 9*H*-carbazol-9-ylacetate **2**. The IR spectrum of product **2** showed a sharp medium absorption bands at 2987, 2865, and 1745 cm^{-1}, which are characteristic bands for aliphatic and carbonyl groups. The ^{1}H NMR spectrum of compound **2** revealed the appearance of triplet at δ 2.10 ppm and quartet at δ 3.96 ppm assigned to CH_2CH_3 group. The reaction of compound **2** with hydrazine hydrate in refluxing ethanol gave 2-(9*H*-carbazol-9-yl)acetohydrazide **3**. Furthermore, reaction of compound **3** with sodium nitrite in conc. HCl gave the diazonium salt **4**. The characteristic IR absorption bands of compound **3** appeared at 3330, 3274 and 1645 cm^{-1} due to NH_2, N–H and C=O groups. The spectrum of compound **3** revealed two D_2O-exchangable singlets at δ 8.21 and 8.84 ppm assigned to one N–H and NH_2 proton (Salimon et al., 2010c). The ^{13}C NMR spectra of compounds **2** and **3** showed signals at δ 169.32 and 171.45, respectively, assigned to C=O groups. Beside this, refluxing of diazonium salt **4** with either acetyl acetone or ethyl acetoacetate in the presence of sodium acetate and by using ethanol as solvent afforded 3-[3-(9*H*-carbazol-9-ylacetyl)triazanylidene]pentane-2,4-dione **5** and ethyl 2-[3-(9*H*-carbazol-9-ylacetyl)triazanylidene]-3-oxobutnoate **6**, respectively (Salimon et al., 2010d). The IR spectrum of compound **5** showed characteristic absorption band at 3234 cm^{-1} due to N–H group besides to carbonyl absorption bands at 1702 and 1645 cm^{-1}. Its ^{1}H NMR spectrum revealed two D_2O-exchangable singlets at δ 8.19 and 8.23 ppm due to two NH protons, in addition to three singlets at δ 2.34, 2.37 and 3.75 ppm assignable for two methyl and one methylene group protons, respectively (Salih et al., 2010; Salimon et al., 2011). The analytical and ^{13}C NMR data are in agreement with the proposed structure. Furthermore, the chemical structure of **6** was established on the basis of its elemental analysis and spectral data. Its IR spectrum showed absorption bands at 3321, 1735, 1718 and 1640 cm^{-1} due to NH and C=O groups (Salimon and Salih, 2010b). Its ^{1}H NMR spectrum displayed triplet band at δ 2.12 ppm and quartet at 3.93 ppm corresponding CH_2CH_3 group. The ^{13}C NMR spectrum was characterized by signals at δ 2.38, 13.61, 13.94 and 18.34 ppm assigned to CH_3, CH_2CH_3 and –C=N– carbons, respectively. The reaction of compound **5** with urea and compound **6** with phenyl hydrazine gave 5-[3-(9*H*-carbazol-9-ylacetyl)triazanylidene]-4,6-dimethyl pyrimidin-2(5*H*)-one **7** and *4*-[3-(9*H*-Carbazol-9-yl acetyl)triazanylidene]-5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one 8, respectively (Salimon et al., 2011a). Structure of **7** was confirmed on the basis of elemental analysis and spectral studies. The IR spectrum showed characteristic amide C=O band at 1645 cm^{-1}. The ^{1}H NMR spectrum showed two singlets at δ 2.23 and 2.49 ppm assigned to methyl group protons (Salih et al., 2011). The elemental analysis and ^{13}C NMR data were consistent with the proposed structure. On the other hand, the structure of compound **8** was confirmed on the basis of its element analysis and spectral data. The IR spectrum showed bands at 3213, 1642 and 1622 cm^{-1} due to NH, C=O and C=N groups, respectively. Its ^{1}H NMR spectrum showed, in addition to the expected signals, singlet signal at δ 2.90 ppm assigned to one methyl group protons.

3.2. Antibacterial evaluation

Antimicrobials are one of a very important category of drug; these classes of drugs are prescribed right from simple infections to the serious diseases and also in life threatening infections like meningitis. So it is quite clear from the spectrum of use that these categories of drugs are very important from medical point of view (Salimon et al., 2009). But microbial resistance towards the drug creates a very serious problem; because of this development of resistance many drugs are now useless which were very effective before. Moreover, the toxic effects produced by these antibiotics are also reducing their significance (Salimon et al., 2010e). So the need for new antimicrobial is always be their. All the newly synthesized compounds were evaluated for their in vitro antibacterial activity against *Staphylococcus aureus* (ATCC 6538), *Bacillus subtilis* (NRRL B-14819) and *Micrococcus luteus* (ATCC 21881) as examples of Gram positive bacteria and *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853)

Table 1 Minimal inhibitory concentration (MIC, μg/mL) of the synthesized compounds against some Gram positive and Gram negative bacterial strains.

Compound	*S. aureus* ATCC 6538	*B. subtilis* NRRL B-14819	*M. luteus* ATCC 21881	*E. coli* ATCC 25922	*P. aeruginosa* ATCC 27853	*K. pneumonia* (clinical isolate)
1	–[a]	–	–	–	–	–
2	3.3	5.3	6.6	21.1	13.1	25.6
3	5.0	4.4	6.2	11.2	15.7	7.4
5	5.1	3.4	7.1	16.5	25.6	7.2
6	3.7	2.9	6.1	18.1	4.1	8.8
7	2.8	2.3	2.9	10.3	21.3	8.3
8	1.1	1.2	3.1	6.4	20.2	23.6
Ampicillin trihydrate[b]	0.2	0.39	0.1	0.3	0.2	0.25

[a] (–): Totally inactive.
[b] Ampicillin trihydrate (standard broad spectrum antibiotic).

Table 2 Minimal inhibitory concentrations (MIC, μg/mL) of the synthesized compounds against some fungal strains.

Compound	*C. albicans*	*C. tropicalis*	*C. krusei*	*A. niger*	*A. fumigatus*	*T. rubrum*
1	–[a]	–	–	–	–	–
2	23.4	–	–	–	19.8	–
3	13.4	–	–	–	–	–
5	20.1	–	–	–	11.4	–
6	17.5	–	–	–	16.2	–
7	10.8	–	–	–	8.7	–
8	9.6	–	–	–	10.3	–
Clotrimazole[b]	3.12	6.25	3.12	12.5	6.25	3.12
Miconazole[c]	6.25	3.12	3.12	6.25	12.5	6.25

[a] (–): Totally inactive.
[b] Clotrimazole (standard broad spectrum antifungal agent).
[c] Miconazole (standard broad spectrum antifungal agent).

and *Klebsiella pneumonia* (clinical isolate) as examples of Gram negative bacteria. Disk diffusion method (Cruickshank et al., 1975; Collins, 1976) was used for determination of the preliminary antibacterial activity. Disks measuring 6.25 mm in diameter were punched from Whatman no.1 filter paper. Batches of 100 disks were dispensed to each screw-capped bottle and sterilized by dry heat at 140 °C for an hour. The tested compounds were prepared with different concentrations using DMSO. 1 mL containing 100 times the amount of chemical in each disk was added to each bottle, which contained 100 disks. Disks of each concentration were placed in triplicate in nutrient agar medium seeded with fresh bacteria separately. The incubation was carried out at 37 °C for 24 h. Ampicillin trihydrate was used as a standard drug at a concentration of 10 μg/mL. Solvent and growth controls were kept and zones of inhibition were noted. From the MIC (μg/mL) data presented in Table 1, it can be seen that the synthesized compounds displayed variable inhibitory effects on the growth of tested Gram positive and Gram negative bacterial strains. Ampicillin trihydrate was used as a reference drug. In general, the tested compounds revealed better activity against the Gram positive rather than the Gram negative bacteria. Among the Gram positive bacteria tested, two strains namely; *S. aureus* and *B. subtilis* showed relatively high sensitivity towards the tested compounds. In this view, compounds **7** and **8** were equipotent to ampicillin against *S. aureus* and *B. subtilis*. With regard to the activity against *M. luteus*, the best activity was displayed by compound **7**. On the other hand, investigation of antibacterial activity of the active compounds against the three tested Gram negative strains revealed that compound **8** was able to produce moderate growth inhibitory activity against *E. coli*. Whereas, compounds **3** and **7,** exhibit mild activity against the same microorganism. Meanwhile, the tested microorganisms *P. aeruginosa* and *K. pneumonia* strains were proved to be weakly sensitive to the tested compounds. Among these, compounds **3** and **6** showed moderate growth inhibitory profiles against these microorganisms.

3.3. Antifungal evaluation

Compounds **1**–**8** screened for their in *vitro* antifungal activity against *Candida albicans*, *Candida tropicalis* and *Candida krusei* as representatives of fungi and *Aspergillus niger*, *Aspergillus fumigatus* and *Tricophyton rubrum* as examples of moulds in DMSO by the serial plate dilution method (Khan, 1997; Varma, 1998). All the fungal and mould strains were clinical isolates, identified with conventional morphological and biochemical methods. Clotrimazole and Miconazole (antifungals) were used as reference drugs. Sabouraud's agar media were prepared by dissolving peptone (1 g), D-glucose (4 g), and agar (2 g) in distilled water (100 ml) and adjusting the pH to 5.7. Normal saline was used to make a suspension of the spore of fungal strain for lawning. A loopful of particular fungal strain was transferred to 3 ml saline to get a suspension

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of the corresponding species. Agar media (20 mL) was poured into each petri dish. Excess suspension was decanted and the plates were dried by placing in an incubator at 37 °C for 1 h. Using an agar punch wells were made into each well labeled. A control was also prepared in triplicate and maintained at 37 °C for 3–4 days. Antifungal activity was determined by measuring the diameter of the inhibition zone. The MIC (μg/mL) values of the tested compounds against the tested fungal strains are recorded in Table 2. Concerning the antifungal activity of the tested compounds, only two organisms namely; *C. albicans* and *A. fumigatus* showed certain sensitivity against some of the tested compounds, whereas the rest of the fungal strains were totally insensitive to the same compounds. Compounds **7** and **8** exhibited moderate growth inhibitory action on *A. fumigatus* and *C. albicans* microorganisms.

4. Conclusion

The antimicrobial results revealed that compound **7** and **8** have promising activities against some tested microorganisms which may be due to the increase the lipophilic character of the molecules, which facilitate the crossing through the biological membrane of the microorganism and thereby inhibit their growth. In conclusion, we reported here a simple and convenient route for the synthesis of some new derivatives based on carbazole moiety for antimicrobial evaluation.

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