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PREPARATION AND EVALUATION OF SUBSTITUTED CARBAZOLE DERIVATIVES AS POSSIBLE ANTIBACTERIAL AGENTS

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ABSTRACT

A series of 1-(9-bromo-1,2-dihydropyrazino[3,2,1-jk]carbazol-3-yl)ethanone, 1-(9-bromo-1,2-dihydropyrazino[3,2,1-jk]carbazol-3-yl)propan-1-one and 1-(9-bromo-1,2-dihydropyrazino[3,2,1-jk]carbazol-3-yl)butan-1-one compounds derived from 9H-carbazole were synthesized via the Suzuki coupling reaction. The derivatives showed very high antimicrobial activity. The prepared compounds identified by spectral methods LCMS, FTIR, ^{1}H-NMR, ^{13}CNMR.

KEYWORDS: "carbazole, bromination, alkyl halides, antimicrobial activity".

1. INTRODUCTION

One of the naturally occurring heterocyclic compounds that possess good biological activities specifically affinity towards DNA is carbazole.[1] The tumour cell cycle can be arrested at the M phase by carbazole.[2] It increases p53 which results the death of apoptotic cell and promotes bcl-2 phosphorylation.[3,4] Hence for the development of antitumor activity using bioisosteric replacements, these compounds play a vital role. Carbazole derivatives are well known for their pharmacological activities. Earlier reports show that the derivatives of carbazole moiety employed in many pharmacological activities, such as antibacterial, antifungal,[5] antitumor, antineoplastic,[6,10] anticonvulsant,[11] antioxidant,[12] antidiabetic,[13] antipsychotic[14] and larvicidal activity.[15]

Photo physical and biological properties of carbazole derivatives are important for its applications. In particular, prominent pharmacological activities of aminocarbazole and its derivatives made them as potential for researchers.[16] For curing Alzheimer's disease, the aminocarbazole derivative has been used as it is active because the presence of an amino group at the indole nucleus has shown promising results as a rehabilitative medicine. 1-aminocarbazoles have been identified as Bcl-2 protein inhibitors, NPY5 antagonists, and anion receptors. Apart from medicinal applications, they are also employed in syntheses of various dyes and pigments, stabilizers for polymers, pesticides, photographic materials and diagnostic reagents in cytochemical studies.[17]

2. MATERIALS AND METHODS

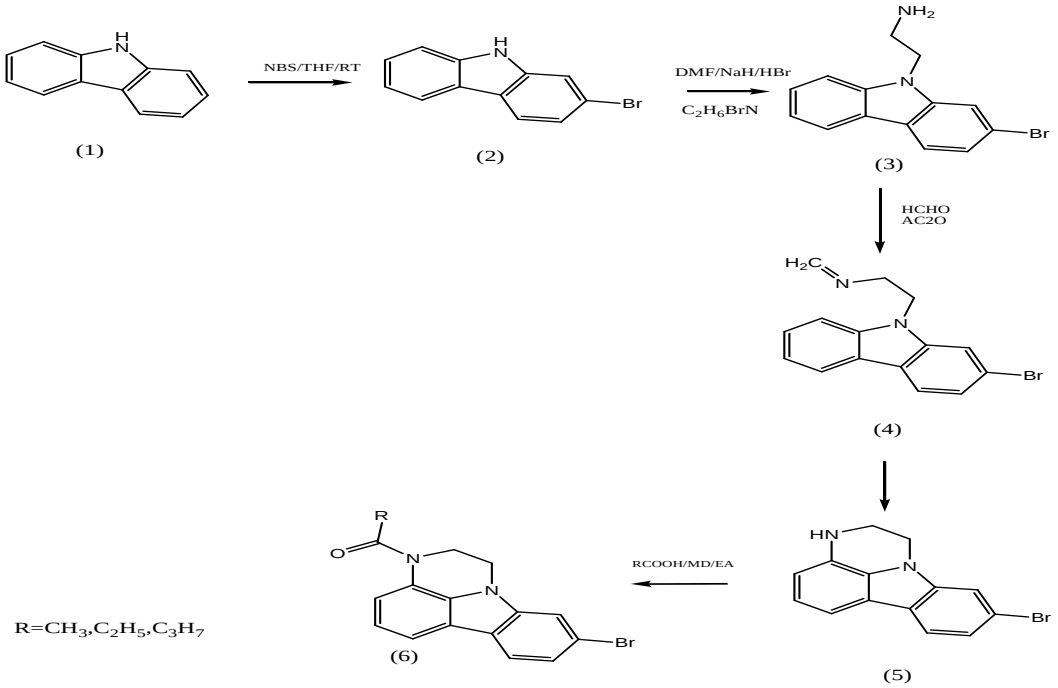
2.1 Scheme

The reaction sequence for different title compounds is shown in Scheme.1. The 9H-carbazole **(1),** as starting material, was prepared according to reported procedure.

Compound **(1)** was subjected to bromination and using NBS, THF to give compound **(2)** with 64% yield. Compound **(2)** was targeted with bromo ethylamine results compound **(3)** with 45% yield. The 2-(2-bromo-9H-carbazol-9-yl)-N-methylene ethanamine **(4)** was prepared by adding formaldehyde and acetic anhydride and the reaction results with 83% yield. Compound **(4)** was then subjected to coupling agent using carbodiimide and it results compound **(5)** with 70% yield. Compound **(5)** was reacted with MD and acetic acid to synthesize compound **(6)**. Substituted carbazole derivatives **(6a-c)** were prepared by the addition of various alkyl halides in dimethylformamide.

2.2. Synthesis of 2-bromo-9H-carbazole (2)

To a stirred 9H-carbazole (5.7 g, 21 mmol) in anhydrous DMF (100 mL) in ice water bath, NBS (11 g, 62 mmol) was added. The mixture was stirred with the help of a magnetic stirrer at room temperature for 24 h, the resulting mixture was poured into ice water (500 mL) and filtrated. Then it was washed with water for three times and recrystallized with toluene/hexane to give 2-bromo-9H-carbazole **(2)** (5.8 g, 64% yield).



Sheme 1: Reaction procedure for title compound.

^{1}H NMR (500 MHz, $CDCl_3$) ppm: 7.30 (d, 1H, Ar-CH), 7.63 (m, 1H, Ar-CH), 7.12 (m, 1H, Ar-CH), 7.64 (d, 1H, Ar-CH), 7.20 (d, 1H, Ar-CH), 7.37 (s, 1H, Ar-CH), 10.12 (s, 1H, NH); ^{13}CNMR (100MHz, DMSO): 129.5, 110.2, 117.5, 105.0, 115.8, 120.5; IR (KBr) cm^{-1}: 779 C-Br, 1517 Ar C=C, 3321 N-H; LCMS m/z (M+1) = 244.28, calcd for $C_{12}H_8BrN$ Mol.wt = 245.1; Anal. calcd for $C_{12}H_8BrN$: C 58.56, H 3.28, Br 32.24, N 5.69. Found: C 57.13, H 3.52, Br 31.21, N 5.29.

2.3. Synthesis of 2-(2-bromo-9H-carbazol-9-yl)ethanamine (3)

To a stirred compound **(2)** (1.0 g, 3.6 mmol) in anhydrous DMF (15 mL), NaH (0.50 g, 4.5 mmol) and bromo ethylamine was added and heated to 110 ◦ C for 0.5 h. For brominating HBr (0.49 g, 3.9 mmol) was added. Again the solution was stirred at 110 ◦C for 24 h, the resulting mixture was poured into ice water (50 mL) and filtrated. Washed with water for three times and the deposit was loaded on to silica gel column with n-hexane/CH_2Cl_2 (1:1, v/v) as eluent to give compound **(3)** (0.62 g, 45% yield).

^{1}H NMR (500 MHz, $CDCl_3$) ppm: 7.00 (d, 1H, Ar-CH), 7.11 (m, 1H, Ar-CH), 7.21 (m, 1H, Ar-CH), 7.78 (d, 1H, Ar-CH), 7.34 (d, 1H, Ar-CH), 7.05 (d, 1H, Ar-CH) 4.09 (T, 2H, CH_2) 2.09 (T, 2H, CH_2) 3.10(m, 2H, NH_2); ^{13}CNMR (100MHz, DMSO): 110.3, 121.2, 130.6, 104.5, 54.9, 40.5; IR (KBr) cm^{-1}: 790.2 C-Br, 2923 alph C-H, 3055 Ar-C-H, 3395 N-H; LCMS m/z (M+1) = 288.17, calcd for $C_{14}H_{13}BrN_2$ Mol.wt = 289.5; Anal. calcd for $C_{14}H_{13}BrN_2$: C 54.55, H 4.62, N 9.65. Found: C 54.51, H 4.65, N 9.59.

2.4. Synthesis of 2-(2-bromo-9H-carbazol-9-yl)-N-methylene ethanamine (4)

Compound **(3)** (1.0 g, 2.3 mmol) and formaldehyde (0.73 g, 5.4 mmol) were dissolved in the mixture of toluene (70 mL) and acetic anhydride (15 mL). The mixture were stirred at 90 ◦ C, the resulting mixture were poured into water and extracted three times with ethyl acetate. The organic layer was subsequently dried over anhydrous sodium sulfate. After removing the solvent under reduced pressure, the residue was loaded on to silica gel column with n-hexane/CH_2Cl_2 (1:1, v/v) as eluent to give Compound **(4)** (0.87 g, 83% yield).

^{1}H NMR (500 MHz, $CDCl_3$) ppm: 7.45 (d, 1H, Ar-CH), 7.53– (m, 1H, Ar-CH), 7.30 (m, 1H, Ar-CH), 7.83 (d, 1H, Ar-CH), 7.15 (d, 1H, Ar-CH), 7.39 (d, 1H, Ar-CH), 7.12 (s, 1H, Ar-CH) 3.90 (t, 2H, CH_2) 3.20 (s, 2H, CH_2) 1.50 (t, 2H, CH_2); ^{13}CNMR (100MHz, DMSO): 130.5, 115.6, 104.4, 55.9, 52.7, 166.8; IR (KBr) cm^{-1}: 780.2 C-Br, 2843 alph C-H, 3058 Ar-C-H, 3388 N-H, 1485 C=N; LCMS m/z (M+1) = 300.06, calcd for $C_{15}H_{13}BrN_2$ Mol.wt = 301.6; Anal. calcd for $C_{15}H_{13}BrN_2$: C 59.82, H 4.35, N 9.30. Found: C 57.81, H 4.54, N 9.13.

2.5. Synthesis of 9-bromo-2,3-dihydro-1H-pyrazino[3,2,1-jk]carbazole (5)

In toluene (90 mL), Compound **(4)** (2.0 g, 4.66 mmol), carbodiimide (1.92 g, 10.8 mmol) were dissolved. The mixture were stirred at 90 ◦ C for 24 h, the resulting mixture were poured into water and extracted three times with ethyl acetate. The organic layer was subsequently dried over anhydrous sodium sulfate. After removing the solvent under reduced pressure, the residue was loaded into silica gel column with n-hexane/CH_2Cl_2 (1:2, v/v) as eluent to give 9-bromo-2,3-dihydro-1H-pyrazino[3,2,1-jk]carbazole **(5)** (1.75 g, 70% yield).

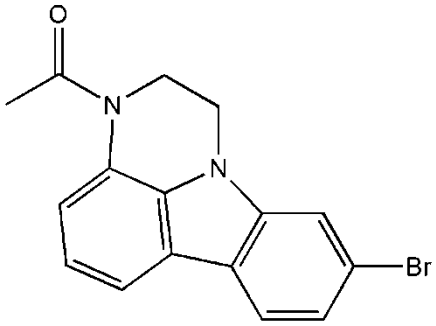
^{1}H NMR (500 MHz, $CDCl_3$) ppm: 6.45 (d, 1H, Ar-CH), 6.53– (m, 1H, Ar-CH), 7.83 (d, 1H, Ar-CH), 7.15 (d, 1H, Ar-CH), 7.39 (d, 1H, Ar-CH), 7.12 (s, 1H, Ar-CH) 3.90 (t, 2H, CH_2) 3.20 (t, 2H, CH_2) 3.50 (d, 2H, NH); ^{13}CNMR (100MHz, DMSO): 130.5, 125.6, 115.6, 104.4, 55.9, 52.7; IR (KBr) cm^{-1}: 788.2 C-Br, 2873 alph C-H, 3058 Ar-C-H, 3388 N-H, 1485 C=N; LCMS m/z (M+1) = 286.06, calcd for $C_{14}H_{11}BrN_2$ Mol.wt = 287.7; Anal. calcd for $C_{14}H_{11}BrN_2$: C 58.56, H 3.86, N 9.76 Found: C 57.41, H 3.89, N 8.58.

2.6. General procedure for the synthesis of substituted carbazole derivatives (6)

Compound **(5)** (0.20 g, 0.44 mmol) and MD (0.28 g, 1.03 mmol) were dissolved in THF (20 mL), then alkyl halides (0.13 g, 1.1 mmol) was added. The solution was stirred at room temperature for 4 h, filtered by adding alcohol, washed by alcohol three times and then dried under vacuum to give compound **(6)** (0.24 g, 79% yield).

2.7. Synthesis of 1-(9-bromo-1,2-dihydropyrazino[3,2,1-jk]carbazol-3-yl)ethanone (6a)

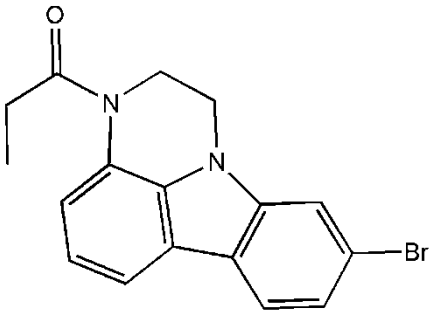
Compound **(6)** (0.20 g, 0.44 mmol) and MD (0.28 g, 1.03 mmol) were dissolved in THF (20 mL), then methyl chloride (0.13 g, 1.1 mmol) was added. The solution was stirred at room temperature for 4 h, filtered by adding alcohol, washed by alcohol three times and then dried under vacuum to give compound **(6a)** (0.24 g, 79% yield).



^{1}H NMR (500 MHz, $CDCl_3$) ppm: 6.25 (d, 1H, Ar-CH), 6.83– (m, 1H, Ar-CH), 7.53 (d, 1H, Ar-CH), 7.35 (d, 1H, Ar-CH), 7.29 (d, 1H, Ar-CH), 7.52 (s, 1H, Ar-CH) 3.98 (t, 2H, CH_2) 3.28 (t, 2H, CH_2) 2.50 (d, 3H, CH_3); ^{13}CNMR (100MHz, DMSO): 130.5, 125.6, 115.6, 104.4, 55.9, 52.7, 167.8, 20.7; IR (KBr) cm^{-1}: 788.2 C-Br, 1672 C=O, 2873 alph C-H, 3058 Ar-C-H, 1585 C-N; LCMS m/z (M+1) = 328.06, calcd for $C_{16}H_{13}BrN_2O$ Mol.wt = 329.7; Anal. calcd for $C_{16}H_{13}BrN_2O$: C 58.38, H 3.98, N 8.51, O 4.86 Found: C 57.81, H 3.79, N 8.28, O 4.43.

2.8. Synthesis of 1-(9-bromo-1,2-dihydropyrazino[3,2,1-jk]carbazol-3-yl)propan-1-one (6b)

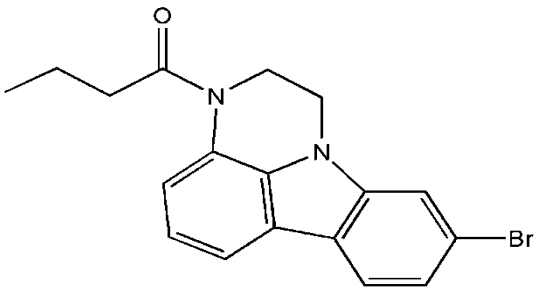
Compound **(6)** (0.20 g, 0.44 mmol) and MD (0.28 g, 1.03 mmol) were dissolved in THF (20 mL), then ethyl chloride (0.13 g, 1.1 mmol) was added. The solution was stirred at room temperature for 4 h, filtered by adding alcohol, washed by alcohol three times and then dried under vacuum to give compound **(6b)** (0.10 g, 36% yield).



^{1}H NMR (500 MHz, $CDCl_3$) ppm: 6.25 (d, 1H, Ar-CH), 6.83– (m, 1H, Ar-CH), 7.53 (d, 1H, Ar-CH), 7.35 (d, 1H, Ar-CH), 7.29 (d, 1H, Ar-CH), 7.52 (s, 1H, Ar-CH) 3.98 (t, 2H, CH_2) 3.28 (t, 2H, CH_2) 2.24 (t, 2H, CH_2) 3.65 (m, 3H, CH_3); ^{13}CNMR (100MHz, DMSO): 132.3, 125.5, 111.9, 114.6, 176.7, 26.9, 51.5; IR (KBr) cm^{-1}: 808.2 C-Br, 1612 C=O, 2973 C-H, 3038 Ar-C-H, 1485 C-N; LCMS m/z (M+1) = 342.4, calcd for $C_{17}H_{15}BrN_2O$ Mol. Wt = 343.3; Anal. calcd for $C_{17}H_{15}BrN_2O$: C 59.43, H 4.41, N 8.61, O 4.66 Found: C 59.39, H 4.48, N 8.12, O 4.10.

2.9. Synthesis of 1-(9-bromo-1,2-dihydropyrazino[3,2,1-jk]carbazol-3-yl)butan-1-one (6c)

Compound **(6)** (0.20 g, 0.44 mmol) and MD (0.28 g, 1.03 mmol) were dissolved in THF (20 mL), then prophyl chloride (0.13 g, 1.1 mmol) was added. The solution was stirred at room temperature for 4 h, filtered by adding alcohol, washed by alcohol three times and then dried under vacuum to give compound **(6c)** (0.25 g, 88% yield).



^{1}H NMR (500 MHz, $CDCl_3$) ppm: 7.25 (d, 1H, Ar-CH), 7.83– (m, 1H, Ar-CH), 7.53 (d, 1H, Ar-CH), 7.35 (d, 1H, Ar-CH), 7.29 (d, 1H, Ar-CH), 7.57 (s, 1H, Ar-CH) 3.88 (t, 2H, CH_2) 0.28 (t, 2H, CH_2) 2.24 (t, 2H, CH_2), 1.64(m, 2H, CH_2), 3.65 (m, 3H, CH_3); ^{13}CNMR (100MHz, DMSO): 132.3, 125.5, 111.9, 114.6, 176.7, 26.9, 51.5, 36.0, 19.6, 50.4; IR (KBr) cm^{-1}: 888.2 C-Br, 1712 C=O, 2973 C-H, 3098 Ar-C-H, 1575 C-N; LCMS m/z (M+1) = 356.4, calcd for $C_{18}H_{17}BrN_2O$ Mol.wt= 357.3; Anal. calcd for $C_{18}H_{17}BrN_2O$: C 60.53, H 4.81, N 7.81, O 4.46 Found: C 59.39, H 4.48, N 8.12, O 4.10.

The synthesized compounds were undergone various characterization to test the suitability of these compounds for pharmaceutical applications. ^{1}HNMR spectra were recorded on a 500 MHz Bruker spectrometer and ^{13}CNMR spectra were recorded on 100 MHz Bruker spectrometer are reported as parts-per-million (ppm) downfield from a tetramethylsilane (TMS) internal standard. Mass spectra were recorded by using Shimadzu mass spectrometer (instrument code: SC/AD/17-005) with 1% HCOOH in water. The FT-IR spectra were recorded in the solid state, as KBr disc by use of a Perkin- Elmer spectrum 100 series FT-IR spectrometer. Column chromatography was performed with silica gel 60-120 mesh (Merck, Mumbai, India.). All the compounds were routinely checked for their reaction on silica gel 60 F254 TLC plates and their spots were visualized by exposing them to UV lamp or iodine vapour. The elemental analysis has been obtained using Varian instrument VARIO EL3 series analyzer. Yield reported is the isolated yield after purification of the compounds.

3. RESULTS AND DISCUSSION

The FT-IR spectra of the entire compounds **6(a-c)** showed absorption band at 1610-1670 cm^{-1} due to -C=O of the compound. This band is missing in compound 1-5 which indicates the coupling agent results the new compound. IR spectra of all the compounds showed (C-Br) at 760-880 cm^{-1}. The absorption bands at 1450-1595 cm^{-1} were attributed to the (C-N) stretch vibrations, which also confirmed the formation of desired carbazole ring in all the compounds.

All the aromatic and aliphatic protons at expected regions were confirmed by ^{1}HNMR. The chemical shift values obtained from ^{13}CNMR for the carbon atoms at 20.17-27.48 ppm (C-16), and about 169.34(C-15), 127.93 ppm (C-12), 51.40-54.45 ppm (C-13) corroborate the compounds of **6(a-c)** characters. The chemical shift values at 120.30-125.89 ppm corroborate the (C-1 to C-11) function. The molecular weight of the newly obtained product was estimated by LCMS report. Elemental analyses ensured the synthesized product and its purity.

3.2 Antimicrobial activities

Preparation of inocula

The test organisms were sub cultured by streaking them on nutrient agar, followed by incubation for 24 h at 37°C. Several colonies of each bacterial species were transferred to sterile nutrient broth. The suspensions were mixed for 15 sec and incubated for 24 h at 37°C on an orbital incubator shaker. Working concentration of the microbial suspension was prepared in 3 ml of sterile saline with turbidity equivalent to 0.5 McFarland scale (i.e., adjusting the optical density to 0.1 at 600 nm), yielding a cell density of 1-2 × 10^{5} CFU/ml.

Antibacterial activity

Nutrient Agar plates were seeded with 8 h broth culture of different bacteria. Sterile paper disc (6 mm in diameter) impregnated with 50 µl of different concentrations of samples were allowed to dry before being placed onto the seeded top layer of the agar plates. Each of the discs was gently placed at equidistance on top of the agar layer to give better contact with agar. The plates were then incubated at 37°C for 24 h. Gentamicin (10µg) was used as positive controls and DMSO/chloroform as negative control. The antibacterial activity was evaluated by measuring the diameter of inhibition zone.

Table: 1 Antibacterial activity of the substituted carbazole derivatives.

(Zone of inhibition in mm, #MIC in µg/mL given in parenthesis)

Compounds (10 µg/ml)	*Staphylococcus aureus*	*Bacillus substilis*	*Escherichia coli*	*Pseudomonas aeruginosa*
6a	18.0(6.25)	20.0(6.25)	20.5(6.25)	22(6.25)
6b	18.5(12.5)	21.0(6.25)	18.5(6.25)	22(6.25)
6c	15.5(6.25)	18.5(6.25)	18.0(6.25)	21.5(6.25)
Gentamicin	20.5(6.25)	21.0(6.25)	20.0(6.25)	23.5(6.25)

MIC: Minimum inhibitory concentration.

The test was performed according the disk diffusion method. All the synthesized carbazole derivatives incorporated with chemotherapeutic pharmacophores were evaluated for their *in vitro* antibacterial activity against two-gram positive bacteria *Bacillus subtilis* and *Staphylococcus aureus* and two gram negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa*.

Almost all the newly synthesized substituted carbazoles showed good antibacterial activity against gram negative bacterial strains *Escherichia coli* and *Pseudomonas aeruginosa* (Plate.1). Results show that compound **6b** and **6c** were most potent against all type of bacterial strains. These compounds contain effective electron donating group which makes it more basic and made efficient as antibacterial agent.

4. CONCLUSIONS

The title compounds were synthesized Suzuki coupling method and the presence of functional groups were analysed by FTIR, ^{1}HNMR and ^{13}CNMR. Molecular weight of these compounds was estimated by LCMS. The purity of the compounds were analysed by elemental analysis. For pharmaceutical applications, the antibacterial activity of these compounds were analysed by disc diffusion method. The results indicate that the compound 6b and compound 6c show better anti bacterial activities compared with compound 6a. This

may be due to the effective electron donating group present in the compounds.

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