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RESEARCH ARTICLE

Synthesis and Biological Evaluation of Novel Carbazole Derivatives

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ABSTRACT

The main objective of this study is to synthesize 2-(substituted phenyl)-3-[{4-(1-naphthyl)-1, 3-thiazol- Considering the biological and chemical relevance of Carbazole containing derivatives, we have devised a novel and efficient synthesis of carbazole derivatives. The series of carbazole derivatives were synthesized in high yield and quality through simple straight forward reaction of 4-(oxiran-2-ylmethoxy)-9H-carbazole with various nucleophiles like piperazine containing heterocyclic derivatives or quinoline derivatives without using any base. The synthesized compounds were confirmed by NMR (^{1}H,^{13}C), IR, Mass spectroscopy, elemental analysis. All the compounds were screened vitro antibacterial activities. The Compound **2a** exhibited good inhibition towards antimicrobial activity compared to the other compounds.

KEYWORDS

4-(oxiran-2-ylmethoxy)-9H-carbazole, Carbazole derivatives, Heterocyclic derivatives, Nucleophiles like piperazine

INTRODUCTION

The carbazole derivatives are well known as β-adrenoreceptor, one common compound is Carvedilol[1-7]. Several synthesis of Carvedilol are been reported in the literature. The innovator's (Boehringer Mannheim GmbH) synthetic approach[8] for the preparation of Carvedilol describes the opening of oxirane ring of 4-(oxiran-2-ylmethoxy)-9H-carbazole, with 2-(2-methoxyphenoxy) ethanamine. The synthesis of various novel carbazole derivatives can easily be prepared by opening of oxirane ring of 4-(oxiran-2-ylmethoxy)-9H-carbazole **(I)** with various nucleophiles like piperazine derivatives and quinoline derivatives **(R)** (Figure 1)[9-12]. These nucleophiles are act as base so there is no need of any extra base to use.

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This is a single step process, also reaction is very clean, fast and obtain in high yield. We aimed our research work towards developing an industrially feasible and cost effective process for the preparation of carbazole derivatives.

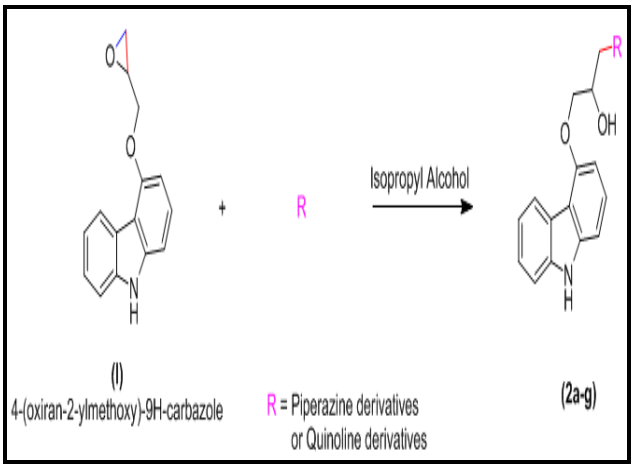


Figure 1: General synthesis of novel carbazole derivatives

EXPERIMENTAL

All reagents were of analytical reagent grade and were used without further purification. The moiety 4-(oxiran-2-ylmethoxy)-9H-carbazole is commercially available and cab easily synthesized.[13-14] Substituents like piperazine derivatives and quinoline derivatives are purchase from Aldrich. Meltingpoints were determined in open capillaries on a Veego (model VMP-D) electronic apparatus and are uncorrected. Thin-layer chromatography was performed on microscope slides (2 cm: 97.5 cm) coated with silica get G for monitoring of the reactions as well as to establish the identity and purity of the compounds. Ethyl acetate:cyclohexane was used as mobile phase and spots were visualized under UV irradiation. Elemental analysis (C, H and N) was performed by Perkin-Elmer, USA, 2400-II CHN analyzer. Mass spectra were obtained with a Agilent LC-MS-6120 mass spectrometer. FTIR spectra (4,000-400 cm^{-1}) were recorded on Shimadzu 8400-S spectrophotometer using KBr disks. Nuclear magnetic resonance spectra were recorded on a Varian 400 MHz spectrometer using DMSO-d_6 as a solvent and TMS as a internal reference (chemical shifts in ppm).

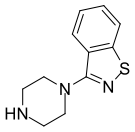
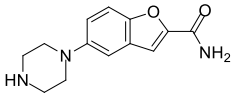
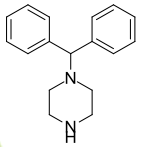
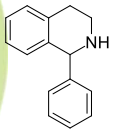
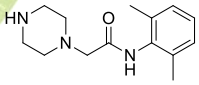
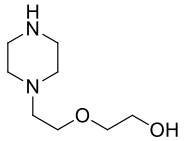
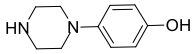
General Procedure for Preparation of Compounds (2a–g)

A mixture of 4-(oxiran-2-ylmethoxy)-9H-carbazole (8.35 mmol), piperazine or quinoline derivatives (R) (8.35 mmol) (Table 1) in isopropyl alcohol (20 mL) were taken in round bottom flask. Their action mixture was heated upto 75-85°C and stirred for 5-8 hours on completion reaction, monitored by TLC (ethyl acetate:cyclohexane = 1:1); the reaction mixture was cool to room temperature. The solid was filtered and washed with isopropyl alcohol to get pure product.

1-((9H-Carbazol-4-yl)oxy)-3-(4-(benzo[d]isothiazol -3-yl)piperazin-1yl)propan-2-ol (2a).

Creamish color solid, Yield 92 %; m.p. 135-138°C; 1H-NMR(400MHz, DMSO-d_6), 10.1(sec, -NH), 8.42(d,1H),8.10-8.12 (t,2H),7.74 (t, 1H), 7.63 (d, 1H), 7.50 (d, 1H), 7.26-7.29 (m, 3H), 7.12-7.19 (m, 2H), 3.96-4.21 (m, 3H), 3.62 (q, 4H), 3.58 (s, -OH), 2.84 (t, 4H), 2.38 (q, 2H); ^{13}C NMR (100 MHz, DMSO-d_6),

Table 1: Isolated yield of compounds **2a–g**

Entry	R (substituent)	Isolated yield (%)
2a		92.0
2b		90.0
2c		95.0
2d		96.0
2e		98.0
2f		95.0
2g		93.0

C= 165.0, 157.0, 149.0, 141.3, 130.2, 124.1, 123.4, 121.3, CH= 128.3, 127.3, 123.2, 121.7, 121.4, 119.8, 111.1, 107.6, 102.7, 64.7, CH_2= 74.6, 60.5, 51.6, 48.0; FTIR (KBr): 3610.5 cm^{-1}(Free C-OH Stretching), 2862.4 cm^{-1} (Aliphatic C-CH Stretching), 1724.2 cm^{-1} (Aromatic C-H Stretching), 1590.8 cm^{-1} (Aromatic C-C Stretching), 1403 cm^{-1} (O-H Banding), 1360 cm^{-1} (Aromatic Ar-NH Stretching), 1305.7 cm^{-1} (Aromatic C-N Stretching), 1260.1 cm^{-1} (Ar-O-R, C-O Stretching), 713.5 cm^{-1} (Mono

substituted Aromatic C-H out of plane); ESI/MS *m/z* 459.58(M+1); Anal. Calc. for $C_{26}H_{26}N_4O_2S$ (458.59): C, 68.10; H, 5.71; N, 12.22; Found: C, 68.2; H, 5.82; N, 12.31.

5-(4-(3-((9H-Carbazol-4-yl)oxy)-2-hydroxypropyl) piperazine-1-yl)benzofuran-2-carboxamide (2b).

Greenish color solid, Yield 90 %; m.p. 221-223°C; ^{1}H-NMR(400MHz, DMSO-d_6), 10.1(sec, -NH), 8.12(d,1H),7.85(s, -NH_2), 7.78(d, 1H), 7.63(t, 1H), 7.48-7.59(t, 3H), 7.12-7.29(m, 4H), 6.5(d, 1H), 3.96-4.21(m, 3H), 3.58(s, -OH), 3.44(t, 4H), 2.84(t, 4H), 2.38(q, 2H); ^{13}C NMR (100 MHz, DMSO-d_6), C= 156, 150.0, 149.0, 146.7, 141.3, 139.2, 131.4, 130.2, 124.1, 121.3, CH= 128.3, 121.7, 121.4, 119.8, 112.4, 111.1, 110.2, 108.9, 107.6, 106.2, 102.7, 64.7, CH_2= 74.6, 64.7, 60.5, 56.3, 56.0; FTIR (KBr): 3605.9 cm^{-1} (Free C-OH Stretching), 3505.5 cm^{-1} (Amide N-H Stretching), 2860.5 cm^{-1} (Aliphatic C-CH Stretching), 1723.8 cm^{-1} (Aromatic C-H Stretching), 1689.7 cm^{-1} (Amide C=O Stretching), 1592.2 cm^{-1} (Aromatic C-C Stretching), 1401.5 cm^{-1} (O-H Banding), 1358 cm^{-1} (Aromatic Ar-NH Stretching), 1308.1 cm^{-1} (Aromatic C-N Stretching), 1262.2 cm^{-1} (Ar-O-R, C-O Stretching), 715.8 cm^{-1} (Mono substituted Aromatic C-H out of plane); ESI/MS *m/z*485.55(M+1); Anal. Calc. for $C_{28}H_{28}N_4O_4$(484.55): C, 69.41; H, 5.82; N, 11.56; Found: C, 69.30; H, 5.71; N, 11.45.

1-((9H-Carbazol-4-yl)oxy)-3-(4-benzhydrylpiperazin-1-yl)propan-2-ol (2c).

White color solid, Yield 95 %; m.p. 151-155°C; ^{1}H-NMR (400MHz,DMSO-d_6), 10.1(sec, -NH), 8.12(d,1H),7.63(d, 1H), 7.50(t, 1H), 7.12-7.37(m, 14H), 5.14(s, 1H), 3.96-4.21(m, 3H), 3.58(s, -OH), 2.63-2.71(m, 6H), 2.35(m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6), C= 149.0, 142.7, 141.3, 130.2, 124.1, 121.3, CH= 129.2, 128.2, 126.3, 121.7, 121.4, 119.8, 111.1, 107.6, 102.7, 84.5, 64.7, CH_2= 74.6, 64.7, 60.5, 58.8, 54.4; FTIR (KBr): 3603.8 cm^{-1} (Free C-OH Stretching), 2862 cm^{-1} (Aliphatic C-CH Stretching), 1725.1 cm^{-1} (Aromatic C-H Stretching), 1595.1 cm^{-1} (Aromatic C-C Stretching), 1405 cm^{-1} (O-H Banding), 1360.4 cm^{-1} (Aromatic Ar-NH Stretching), 1263.1 cm^{-1} (Ar-O-R, C-O Stretching), 714 cm^{-1} (Mono substituted Aromatic C-H out of plane); ESI/MS *m/z* 492.62(M+1); Anal. Calc. for $C_{32}H_{33}N_3O_2$ (491.62): C, 78.18; H, 6.77; N, 8.55; Found: C, 78.08; H, 6.68; N, 8.45.

1-((9H-Carbazol-4-yl)oxy)-3-(1-phenyl-3,4-dihydro isoquinolin-2(1H)-yl)propan-2-ol (2d).

An off-white color solid, Yield 96 %; m.p. 162-165°C; ^{1}H-NMR(400MHz,DMSO-d_6), 10.1(sec, -NH), 8.12(d,1H),7.63(d, 1H), 7.50(t, 1H), 7.12-7.29(m, 13H), 5.19(s, 1H), 4.21(m, 2H), 3.96(m, 1H), 2.74-2.77(m, 4H), 2.38(q, 2H); 13C NMR (100 MHz, DMSO-d6), C= 149.0, 143.5, 142.7, 141.3, 133.4, 130.2, 124.1, 121.3, CH= 129.2, 128.3, 128.2, 126.4, 126.2, 126.1, 126.0, 121.7, 121.4, 119.8, 111.1, 107.6, 102.7, 65.0, 64.4, CH_2= 74.6, 65.0, 55.4, 50.7, 27.3; FTIR (KBr): 3611.4 cm^{-1} (Free C-OH Stretching), 2900 cm^{-1} (Aliphatic C-CH Stretching), 1680 cm^{-1} (Aromatic C-H Stretching), 1585.2 cm^{-1} (Aromatic C-C Stretching), 1407.1 cm^{-1} (O-H Banding), 1359.1 cm^{-1} (Aromatic Ar-NH Stretching), 1265.2 cm^{-1} (Ar-O-R, C-O Stretching), 723.1 cm^{-1} (Mono substituted Aromatic C-H out of plane); ESI/MS *m/z*449.56(M+1); Anal. Calc. for $C_{30}H_{28}N_2O_2$ (448.56); C, 80.33; H, 6.29; N, 6.25; Found: C, 80.28; H, 6.21; N, 6.20.

2-(4-(3-((9H-Carbazol-4yl)oxy)-2-hydroxypropyl)piperazine-1-yl)-N-(2,6-dimethylphenyl)-acetamide (2e).

An off-white color solid, Yield 98 %; m.p. 172-174°C; ^{1}H-NMR(400MHz,DMSO-d6), 10.1(sec, -NH), 8.12(d,1H),7.63(d, 1H), 7.50(t, 1H), 7.12-7.29(m, 7H), 7.23(s, -NHCO), 4.21(m, 2H), 3.96(m, 1H), 3.58(s, -OH), 3.34(s, 2H), 2.63-2.71(m, 6H), 2.35(m, 4H), 2.12(s, 6H); C= 168.5, 149.0, 141.3, 137.1, 130.7, 130.2, 124.1, 121.3, CH= 128.3, 127.7, 126.8, 121.7, 121.4, 119.8, 111.1, 107.6, 102.7, 64.7, CH_2= 74.6, 63.6, 60.5, 57.8, 55.5, CH_3= 17.6; 36101 cm^{-1} (Free C-OH Stretching), 3442.2 cm^{1} (Amide N-H Stretching), 2989.2 cm^{-1} (Aliphatic C-CH Stretching), 1770 cm^{-1} (Aromatic C-H Stretching), 1685 cm^{-1} (Amide C=O Stretching), 1601.1 cm^{-1} (Aromatic C-C Stretching), 1405

cm^{-1} (O-H Banding), 1360 cm^{-1} (Aromatic Ar-NH Stretching), 1310.5 cm^{-1} (Aromatic C-N Stretching), 1265.6 cm^{-1} (Ar-O-R, C-O Stretching), 810 cm^{-1} (meta disubstituted Aromatic C-H out of plane), 720 cm^{-1} (Mono substituted Aromatic C-H out of plane); ESI/MS *m/z*487.61(M+1); Anal. Calc. for $C_{29}H_{34}N_4O_3$(486.61); C, 71.58; H, 7.04; N, 11.51; Found: C, 71.6; H, 7.07; N, 11.58.

1-((9H-Carbazol-4-yl)oxy)-3-(4-(2-(2-hydroxyethoxy) ethyl)-piperazin-1-yl)propan-2-ol (2f).

An off-white color solid, Yield 95 %; m.p. 268-270°C; ^{1}H-NMR(400MHz,DMSO-d_6), 10.1(sec, -NH), 8.12(d,1H),7.63(d, 1H), 7.50(t, 1H), 7.26-7.29(q, 2H), 7.19(d, 1H)), 7.16(d, 1H), 4.21(m, 2H), 3.96(m, 1H), 3.56-3.65(m, 6H), 3.44(t, 2H), 2.63-2.71(m, 6H), 2.51(t, 2H), 2.35(m, 4H); C= 149.0, 141.3, 130.2, 124.1, 121.3, CH= 128.3, 121.7, 121.4, 119.8, 111.1, 107.6, 102.7, 64.7, CH_2= 74.6, 70.0, 69.8, 64.7, 61.3, 60.5, 58.5, 58.2, 50.8; FTIR (KBr): 3640 cm^{-1} (Free C-OH Stretching), 3005.1 cm^{-1} (Aliphatic C-CH Stretching), 1628.1 cm^{-1} (Aromatic C-H Stretching), 1585.2 cm^{-1} (Aromatic C-C Stretching), 1410.1 cm^{-1} (O-H Banding), 1360 cm^{-1} (Aromatic Ar-NH Stretching), 1268.5 cm^{-1} (Ar-O-R, C-O Stretching), 714 cm^{-1} (Mono substituted Aromatic C-H out of plane); ESI/MS *m/z*414.51(M+1); Anal. Calc. for $C_{23}H_{31}N_3O_4$ (413.51); C, 66.81; H, 7.56; N, 10.16; Found: C, 66.7; H, 7.42; N, 10.08.

4-(4-(3-((9H-Carbazol-4-yl)oxy)-2-hydroxypropyl) piperazine-1-yl)phenol (2g).

An off-white color solid, Yield 90 %; m.p. 141-146°C; ^{1}H-NMR(400MHz,DMSO-d_6), 10.1(sec, -NH), 8.12(d,1H),7.63(d, 1H), 7.50(t, 1H), 7.26-7.29(q, 2H), 7.19(d, 1H)), 7.16(d, 1H), 6.77(d, 2H), 6.59(d, 2H), 5.35(s, -ArOH), 4.21(m, 2H), 3.96(m, 1H), 3.58(s, -OH), 3.44(t, 2H), 2.84(t, 4H), 2.63(m, 2H); C= 149.0, 148.0, 146.6, 141.3, 130.2, 124.1, 121.3, CH= 128.3, 121.7, 121.4, 119.8, 116.8, 115.7, 111.1, 107.6, 102.7, 64.7, CH_2= 74.6, 70.0, 60.5, 56.0, 56.3; FTIR (KBr): 3602.2 cm^{-1} (Free C-OH Stretching), 2980.6 cm^{-1} (Aliphatic C-CH Stretching), 1630.5 cm^{-1} (Aromatic C-H Stretching), 1595 cm^{-1} (Aromatic C-C Stretching), 1425.4 cm^{-1} (O-H Banding), 1361.2 cm^{-1} (Aromatic Ar-NH Stretching), 1270 cm^{-1} (Ar-O-R, C-O Stretching), 1205 cm^{-1} (phenol C-O Stretching), 713.2 cm^{-1} (Mono substituted Aromatic C-H out of plane); ESI/MS *m/z*418.50(M+1); Anal. Calc. for $C_{25}H_{27}N_3O_{33}$ (417.50); C, 71.92; H, 6.52; N, 10.06; Found: C, 71.82; H, 6.45; N, 9.98.

RESULTS AND DISCUSSION

The synthesis of these heterocyclic compounds usually carried out in polar protic solvents such as DMSO, DMF and water. The choice of solvent is main key step for synthesis of organic reactions. So we first looked in selection solvents and Isopropyl Alcohol is selected for synthesis. The elemental analysis data showed good agreement between the experimentally determined values and the theoretically calculated values within the limits of permissible error. Yield and substitution of the synthesized compounds are listed Table 1.

Biological Evaluation

Antibacterial Activity

Antibacterial activity of the synthesized compounds was determined against Gram-positive bacteria (*Bacillus subtilis and Staphylococcus aureus*) and Gram-negative bacteria (*Escherichia coli and Xanthomonas malvacearum*) in DMF by disc diffusion method on nutrient agar medium[15]. The sterile medium (nutrient agar medium, 15mL) in each petri plates was uniformly smeared with cultures of Gram-positive and Gram-negative bacteria. Sterile discs of 10mm diameter (Hi-Media) were made in each of the petri plates to which 50 µL (1mg/mL, that is, 50µg/disc) of the different synthesized compounds was added. The treatments also included 50 µL of DMF as negative control and streptomycin (1 mg/mL; 10µg/disc) as positive control for comparison. For each treatment, three replicates were maintained. The plates were incubated at 37 ± 2°C for 24 h, and the size of the resulting zone of inhibition, if any was determined. The investigation of antibacterial screening data revealed that synthesized compounds showed

comparable activity against *Bacillus subtilis*, *Staphylococcus aureus*, and *Escherichia coli*. Compound **2a** exhibited good activity with the zone of inhibition in the range of 16 mm against pathogenic bacteria strain.

Antifungal Activity

The synthesized compounds were screened for the antifungal activity against *Fusariumoxys-porum*in DMF by poisoned food technique[16]. Potato dextrose agar(PDA)media were prepared, and about 15mL of PDA was poured into each petri plate and allowed to solidify 5mm disc of seven-day-old culture of the test fungi was placed at the center of the petri plates and incubated at 26°C for 7 days. After incubation, the percentage inhibition was measured and three replicates were maintained for each treatment. Nystatin was used as standard. All the synthesized compounds and nystatin were tested (at the dosage of 500 µL of the compounds/petri plate, where concentration was 0.1 mg/mL) by poisoned food technique.

The antifungal activity of synthesized compounds was evaluated and compared with standard drug nystatin.

All the synthesized compounds showed moderate inhibitory activity and compound-**2c** showed good anti-fungal activity with the 56.4% inhibition against *F.oxyspo- rum*, compared to other compound.

Among the synthesized compounds, inhibitory activity is in the order of **2a**>**2b–f** >**2g** against tested fungi. Antimicrobial screening results of the tested compounds are shown in Table 2.

CONCLUSION

We have demonstrated that reaction of 4-(oxiran-2-ylmethoxy)-9H-carbazole with various nucleophiles like piperazine derivatives and quinoline derivative, which enables efficient synthesis in a single step with satisfactory yield. The products of this reaction are of potential medicinal interest.

Table 2: *In-Vitro* antibacterial and antifungal activities of synthesized compounds
Diameter of inhibition zone (mm) % inhibition

	B. subtilis	***S. aureus***	***X. malvacearum***	***E. coli***	***F. oxysporum***
2a	13	15	16	14	56.1
2b	14	11	11	12	47.2
2c	13	12	11	11	51.3
2d	11	17	11	13	52.7
2e	11	14	12	13	41.9
2f	13	15	14	14	44.6
2g	11	12	13	13	43.2
Streptomycin	18	20	18	19	—
Nystatin	—	—	—	—	85.2

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