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DESIGN, SYNTHESIS, AND BIOLOGICAL ACTIVE STUDY OF NOVEL AMIDE-COUPLED 6-HYDROXY-N-PHENYL-9H-CARBAZOLE-3-CARBOXAMIDE PROMOTED BY COPPER HALIDE

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ABSTRACT

The development of antimicrobials having a unique mode of action is an essential to solve problems of multi-drug resistance challenges. Here in, we have designed and synthesized novel amide-coupled 6-hydroxy-N-phenyl-9H-carbazole-3-carboxamide (6a-f) by acid-amine coupling reaction of 6-hydroxy-9H-carbazole-3-carbonyl chloride with substituted various amines in the presence of strong base. The synthesized amide-coupled naphthalene scaffolds were characterized through ^{1}H NMR; ^{13}C NMR, FT-IR as well as mass spectroscopic techniques. These derivatives were examined for their antimicrobial. Among all, "6d & 6e "exhibited excellent antibacterial activity at minimum inhibitory concentration (MIC) values ranging between 12.5 and 100 µg/mL against Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and Streptococcuspyogenes compared to standard drug Ciprafloxin. The antifungal assay revealed that compounds 6e wsa most effective (MIC - 250 µg/mL) against Candida albicans compared to standard drug Fluconazole.

KEYWORDS: 6-hydroxy-9H-carbazole-3-carboxylic acid, 6-hydroxy-9H-carbazole-3-carbonyl chloride, 6-hydroxy-N-phenyl-9H-carbazole-3-carboxamide, Bioevluation.

1. INTRODUCTION

Amides are one of the most important functional groups in organic synthesis and medicinally chemistry due to their presence in numerous interesting compounds such as naturally occurring molecules, peptides, pharmaceutical agents, proteins and alkaloids, among others. This synopsis surveys the diverse recent approaches to amide synthesis from non-activated carboxylic acids and derivatives as well as noncarboxylic compounds, highlighting the most

innovative methodologies and those that are more eco-friendly compared to traditional methods while focusing on recent developments during the past two years. The development of efficient as well as convenient methods for the synthesis of amides has been a central goal in synthetic chemistry because of their prevalence in synthetic chemistry and the life sciences.[1–10]

A major dispute of modern chemistry is the plan of new chemical reaction successions that supply novel compounds in high yields. Amides are an incredibly vital group of organic compounds with a variety of functions. Some derivatives of amides reveal biological properties such as anti-inflammatory agents,[11] Antioxidant Activity,[12] anticancer activity,[13] fungicide and antibacterial,[14-17] H1-receptor antagonists.[18] The conventional approach for the synthesis of amides coupling is the reaction of carboxylic acids with amines at high temperature. Because of carboxylic acid's low activity, several procedures for their activation have been reported in the literature. Negative aspects of these procedures consist of modest yields, by products, costly coupling reagents and difficulty in removal of surplus reagents. Consequently, the growth of a new and uncomplicated synthetic procedure for the preparation of amides has become an interesting challenge.

In this study, we report synthesis of 6-hydroxy-N-phenyl-9H-carbazole-3-carboxamide based derivatives **(5a-f)** via amide bond formation between 6-hydroxy-9H-carbazole-3-carbonyl chloride and different substituted amines having various substituents such as nitro, halogen, methoxy etc. The synthesized amide-coupled 6-hydroxy-N-phenyl-9H-carbazole-3-carboxamide scaffolds were characterized through 1H NMR, 13C NMR, and FT-IR as well as mass spectroscopic techniques. The scaffolds were evaluated for their antibacterial and antifungal potential. For any derivatives of potential therapeutic, it is an important to determine plausible molecular weight of target compounds that can bind efficiently and accuracy its activity. In many studies, it has been exhibited that different carbazoles scaffolds can inhibit bacterial and fungal.

2. METHODS AND MATERIALS

All the chemicals, synthetic grade reagents, and solvents were purchased from commercially and they were used without further purification. The standard procedures were used to follow by dry solvents and reaction mixture were checked by thin-layer chromatography (n-hexane: Ethylacetae) on silica gel plates coated with alumina. The melting points of the titled compounds were determined in open capillary tubes and were uncorrected. ^{1}HNMR and ^{13}C-

NMR spectrum were recorded titled derivatives on a Bruker DRX-400MHz and 100MHz instrument using $CDCl_3$ as a solvent. The chemical shifts, δ, are given in ppm downfield and up field from the internal standard Tetramethylsilane. The splitting patterns titled compounds are designated as follows; s: singlet; d: doublet and m: multiplet. The mass spectra were obtained on a Shimadzu 2010A LCMS spectrometer. Elemental analysis of the derivatives was recorded by the instrument.

2.1. Preparation of 6-hydroxy-9H-carbazole-3-carboxylic acid (3)

The mixture of p-amino benzoic acid (1mmol), p-benzoquinone (2mmol) dissolved in acetonitrile in a dry and clean four neck RBF. The copper iodide and caesium carbonate added in RBF. The total set up arranged on the magnetic stirrer and was maintained 12hrs at 100^0C. The reaction mixture was monitored by TLC (5:5-Ethyl acetate: n-hexane).After completion of the reaction, catalyst was filtered and the reaction mixture poured into ethyl acetate and washed solution of sodium bi carbonate. The organic layer separated kept side and aqueous layer washed with (2x10mL) after separated. Both of the organic layers combined distilled off u/vacuum. Crude product was separated by columns chromatography and recrystallization from ethanol.

Characterisation

Pale brown solid; Yield-92%, Rf: - 0.54 (n-hexane: EtOAc: 5:5); IR (KBr cm-1): 3568, 3345, 3058, 2564, 1687, 1602, 1578, 1546, 1512, 1245,812;^{1}HNMR(400MHz,$CDCl_3$) ppm:11.825 (s, 1H,-COOH), 11.172 (s,1H, NHCO-), 8.894 (s, 1H, -OH), 8.712 (s, 1H, Ar-H),8.216 (d, J= 5.4 Hz, 1H, Ar-H), 7. 485 (d, J=6.8Hz, 1H, Ar-H), 7.482 (s,1H,Ar-H), 7.284 (d, J= 7.6Hz, 1H, Ar-H), 6.962 (d, J= 7.2Hz, 1H, Ar-H);^{13}CNMR (100MHz, $CDCl_3$) ppm: 170.21, 149.73, 138.39,135.64, 129.07,123.55,120.66, 114.94, 113.02, 11.96, 109.75, and 102.44;LCMS (m/z):226.56 (M-H);Molecular formulae: $C_{13}H_9NO_3$;Elemental analysis: Calculated: C- 68.72, H- 3.94, N- 6.16; Obtained: C- 68.64, H- 3.97 ,N-6.24.

2.2. Preparation of 6-hydroxy-9H-carbazole-3-carbonyl chloride (4)

Take clean and dry 25mL four necks RBF.25mL methylene dichloride taken in a RBF and 6-hydroxy-9H-carbazole-3-carboxylic acid (1mmol) is dissolved in solvent. The thionyl chloride added drop wise with help of dropping funnel in a RBF in 5-10^0C. The total arrangement fitted on the magnetic stirrer. The reaction is continued in 2 hrs. at reflux. After completion of the reaction time, the mixture cooled under tap water and evaporated the unreacted thionyl chloride and proceeded to the further reaction.

Characterisation

Orange red solid; Yield-85%, Rf: - 0.52 (n-hexane: EtOAc: 5:5); IR (KBr cm-1): 3572, 3358, 3057, 1675, 1575, 1541, 1520, 1239,824;^{1}HNMR (400MHz, $CDCl_3$) ppm: 11.128 (s, 1H, NH-indole), 8.924 (s, 1H, -OH), 8.845 (s, 1H, Ar-H), 8. 184 (d, J= 8.8 Hz, 1H, Ar-H), 7. 567 (d, J= 8.0Hz, 1H, Ar-H), 7.477 (s, 1H, Ar-H), 7.276(d, J= 7.6Hz, 1H, Ar-H), 6. 894 (d, J= 7.2Hz, 1H, Ar-H);^{13}CNMR (100MHz, $CDCl_3$) ppm: 169.98, 150.09, 148.44, 139.53, 129.71, 128.06,124.72, 121.02, 115.38, 113.56, 112.45, 102.62;; LCMS (m/z):247.17 (M+H);Molecular formulae: $C_{13}H_8ClNO_2$; Elemental analysis: Calculated: C- 63.56, H- 3.28, N- 5.70; Obtained: C- 63.48, H- 3.26 , N- 7.78.

2.3. Preparation of (1) 6-hydroxy-N-phenyl-9H-carbazole-3-carboxamide Derivatives (6a-f)

Take clean and dry 25mL four necks RBF.25mL methylene dichloride taken in a RBF and 6-hydroxy-9H-carbazole-3-carbonyl chloride (1.25 mmol) is dissolved in a solvent and substituted anilines added the above solution and strong base such as trimethyl amine is addition to in the solution. The total arrangement fitted on the magnetic stirrer. The reaction is continued in 2 hrs. at reflux. The reaction mixture checked by the TLC (EtOAc: n-hexane-4:6) after completion of the reaction time, the mixture cooled under tap water and neutralized with 2NHCl. The completion of the neutralization, ethyacetate added to the solution and separated the organic layer and washed with water in thrice. The final compound distilled off under vacuumed and desired compound can be obtained.

2.3.1.6-hydroxy-N-phenyl-9H-carbazole-3-carboxamide (6a)

Orange red solid; Yield-87%, Rf: - 0.50 (n-hexane: EtOAc: 6:4); IR (KBr cm-1): 3547, 3312, 3037, 1678, 1576, 1543, 1525, 1229,823;^{1}HNMR (400MHz, $CDCl_3$) ppm: 10.842 (s, 1H, NH-indole), 10.035 (s, 1H, -CONH), 8.942 (s, 1H, -OH), 8.572 (s, 1H, Ar-H), 7.856-7.542 (m, 4H, Ar-H), 7. 493 (s,1H, Ar-H), 7.348-7.265(m,3H,Ar-H),7.102 (m,3H, Ar-H); ^{13}CNMR(100MHz,$CDCl_3$)ppm:165.41,150.09,139.66,135.72,133.69,129.49,128.96,128.45,127.75,125.68,122.31,120.09,113.74, 112.02, 111.82, 109.94, 101.86.LCMS (m/z): 301.66(M-H); Molecular formulae: $C_{19}H_{14}lN_2O_2$; Elemental analysis: Calculated: C-75.48, H- 4.67, N-9.27; Obtained: C- 75.40, H- 4.25, N- 9.35.

2.3.2.6-hydroxy-N-(4-methoxyphenyl)-9H-carbazole-3-carboxamide (6b)

Yellow solid ; Yield-88%, Rf: - 0.54 (n-hexane : EtOAc :6:4) ; IR (KBr cm-1): 3524, 3341, 3056, 1687, 1572, 1534, 1515, 1232,822 ;^{1}HNMR (400MHz, $CDCl_3$) ppm: 11.145 (s, 1H,

NH-indole), 10.215 (s, 1H,-CONH-),9.077 (s, 1H, -OH), 8.509 (s, 1H, Ar-H), 8. 126 (d, J= 8.0 Hz, 1H, Ar-H), 7. 585 (d, J= 9.0Hz, 1H, Ar-H),7.523(d, J= 6.8 Hz, 2H, Ar-H), 7.489 (s, 1H, Ar-H), 7.296(d, J= 6.4 Hz, 1H, Ar-H), 7.125-6.746(m,3H Ar-H) , 3.664(s,3H,-OCH_3) ; ^{13}CNMR (100MHz, $CDCl_3$) ppm: 163.74, 152.85, 148.66, 139.17, 135.68, 129.16, 128.18,126.72, 122.32, 120.64, 115.33, 113.78, 111.74, 110.61,102.74, 56.67.LCMS (m/z): 333.43 (M+H);Molecular formulae: $C_{20}H_{16}lN_2O_3$; Elemental analysis: Calculated: C- 72.21, H- 4.85, N- 8.43; Obtained: C- 72.21, H- 4.84, N- 8.49.

2.3.3. N-(4-chlorophenyl)-6-hydroxy-9H-carbazole-3-carboxamide (6c)

Brown solid ; Yield-90%, Rf: - 0.48 (n-hexane : EtOAc :6:4) ; IR (KBr cm-1): 3529, 3339, 3059, 1681, 1573, 1535, 1519, 1236, 805; ^{1}HNMR (400MHz, $CDCl_3$) ppm: 11.196 (s, 1H, NH-indole), 10.045 (s, 1H,-CONH-), 9.129 (s, 1H, -OH), 8.546 (s, 1H, Ar-H), 8. 152 (d, J= 7.6 Hz, 1H, Ar-H),7.682 (d, J= 8.0 Hz,1H, Ar-H), 7.493(s,1H Ar-H), 7.3677.284(m, 4H, Ar-H);^{13}CNMR(100MHz,$CDCl_3$)ppm:166.19,150.64,139.55,136.55,133.09,131.29,129.66,128.88,128.32,127.02,122.44,120.36,118.56,113.38,111.64,109.46;LCMS(m/z):338.39 (M+2); Molecular formulae: $C_{19}H_{13}ClN_2O_2$; Elemental analysis: Calculated: C- 67.76, H- 3.89, N- 8.32; Obtained: C- 67.68, H- 3.87, N- 8.41.

2.3.4. N-(4-bromophenyl)-6-hydroxy-9H-carbazole-3-carboxamide (6d)

Brown red ; Yield- 90%, Rf: - 0.53 (n-hexane : EtOAc :6:4) ; IR (KBr cm-1): 3515, 3332, 3049, 1685, 1579, 1536, 1516, 1233, 821 ; ^{1}HNMR (400MHz, $CDCl_3$) ppm: 11.194 (s, 1H, NH-indole), 10.042 (s, 1H,-CONH-), 9.113 (s, 1H, -OH), 8.592 (s, 1H, Ar-H), 8. 148 (d, J= 8.8 Hz, 1H, Ar-H), 7. 684 (d, J= 8.0 Hz, 1H, Ar-H), 7.612-7.558(m, 4H, Ar-H), 7.507 (s, 1H, Ar-H), 7.294-7.124 (m, 2H, Ar-H); ^{13}CNMR (100MHz, $CDCl_3$) ppm: 166.29,150.45, 140.08, 137.96, 132.19, 129.17, 128.65, 126.72, 125.33, 123.22, 121.32, 120.09, 114.36, 112.02,110.72, 102.66.LCMS (m/z): 382.43 (M+H); Molecular formulae: $C_{19}H_{13}BrN_2O_2$; Elemental analysis: Calculated: C- 59.86, H-3.44, N- 7.35; Obtained: C- 59.78, H- 3.42, N- 7.42.

2.3.5.6-hydroxy-N-(4-nitrophenyl)-9H-carbazole-3-carboxamide (6e)

Brown red ; Yield-84%, Rf: - 0.50 (n-hexane : EtOAc :6:4) ; IR (KBr cm-1): 3542, 3312, 3052, 1683, 1570, 1533, 1519, 1230, 822 ; ^{1}HNMR (400MHz, $CDCl_3$) ppm: 11.172 (s, 1H, NH-indole), 10.306 (s, 1H,-CONH-), 9.046 (s, 1H, -OH), 8.623 (s, 1H, Ar-H), 8. 186 (d, J= 7.6 Hz, 1H, Ar-H), 7. 942 (d, J= 8.0 Hz, 1H, Ar-H), 7.886(d, J= 6.4 Hz, 1H, Ar-H), 7.564(d,J=6.8Hz,1H,Ar-H);^{13}CNMR(100MHz,$CDCl_3$)ppm:169.71,151.23,141.02,140.36,

138.48,136.65,129.96,129.17,128.96,128.22,127.62,122.45,120.34,113.57,111.76,110.68, 109.74,101.90. LCMS (m/z):347.26 (M+); Molecular formulae: $C_{19}H_{13}lN_3O_4$; Elemental analysis: Calculated: C- 66.70, H-3.77, N-12.10; Obtained: C- 66.62, H- 3.75, N-12.18.

2.3.6.6-hydroxy-N-(thiophen-2-yl)-9H-carbazole-3-carboxamide (6f)

White solid ; Yield-90%, Rf: - 0.45 (n-hexane : EtOAc :5:5) ; IR (KBr cm-1): 3512, 3336, 3049, 1685, 1576, 1545, 1522, 1232, 812 ; 1HNMR (400MHz, CDCl3) ppm: 11.054 (s, 1H, NH-indole), 10.125 (s, 1H,-CONH-), 9.095 (s, 1H, -OH), 8.513 (s, 1H, Ar-H), 8. 154 (d, J= 8.0 Hz, 1H, Ar-H), 7. 940 (d, J= 8.8 Hz, 1H, Ar-H), 7.754-7.364 (m, 3H, Ar-H), 7.310(m,3H,Ar-H);^{13}CNMR(100MHz,$CDCl_3$)ppm:166.65,150.54,140.25,138.36,136.77, 133.88,129.54,129.05,128.68,126.22,124.62,121.45,120.34,118.57,112.72,110.68,108.94, 101.55. LCMS (m/z):309.27 (M+H); Molecular formulae: $C_{17}H_{12}N_2O_2S$; Elemental analysis: Calculated: C- 66.22, H-3.92, N-9.08; Obtained: C- 66.12, H- 3.90, N-9.18.

3. Biological activity

3.1. Antibacterial Activity

The *in vitro* antibacterial activity of the titled compounds enhanced viz; 6-hydroxy-N-phenyl-9H-carbazole-3-carboxamide (6a-f) and its derivatives have being examined in vitro for its potent active bacterial strains such as, S. aureus and Escherichia coli. The *in vitro* activities of these compounds were examined using agar plates and that having in nutrient broth for bacteria. The test compounds were evaluated against each microbial species. The in vitro antibacterial potent activities of the newly prepared derivatives have being compared with standard drug is Ciprafloxin. The antimicrobial inhibitions of the tested compounds are measured as the area of zone of inhibition and summarized in Table-1. This marked and antibacterial activity may be due to the responsibility of high hydrophobic nature of these titled derivatives. The desired compounds possess derivatives segments are more extensive active against bacteria strains and fungal strains. Presumptively due to the strong interaction of the later with the agar medium, this hinders their diffusion in agar medium.

3.2. Antifungal activity

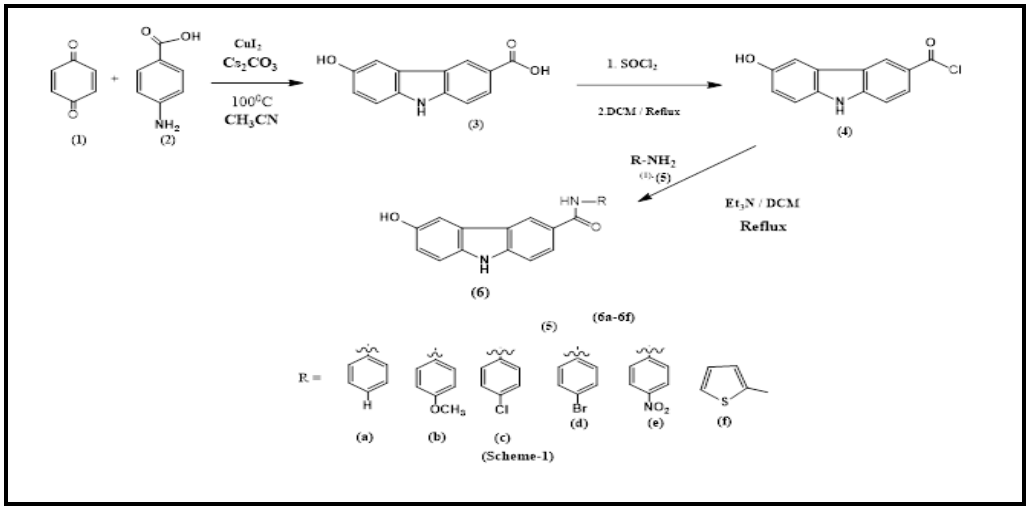
In vitro antifungal screening against A.niger and Candida albicans was used as test strain. The tested derivatives were dissolved in dimethyl sulfoxide (DMSO) and prepare to concentration of 10 mg/mL. Antifungal activity of these compounds was performed by broth micro dilution method. The absorbance was recorded at 530 nm in order to yield the desired transmittance of 70 to 75%. The tested fungal culture was prepared from the stock fungal

culture, a 1:1000 dilution with broth (e.g. 10 µL stock fungal culture: 10 µL broth) was prepared. Sabouraud maltose broth was used as the growth medium and modified antifungal susceptibility testing is based on references drug. Finally all the wells were filled with 100 µL of working fungal culture. **Fluconazole** is used as a reference in the antifungal test. Wells containing serial dilution of DMSO and broth were prepared as control tests. The plate was sealed and incubated at 37 °C for 24 to 48h. The minimum inhibitory concentration (MIC) values of tested derivatives were measured by reading the lowest concentration of compound in the well showing no growth.

4. RESULTS AND DISCUSSION

4.1. Chemistry

In the present investigation of the novel derivatives a series of 6-hydroxy-N-phenyl-9H-carbazole-3-carboxamide (6a-f).These derivatives were synthesized from 6-hydroxy-9H-carbazole-3-carbonyl chloride and substituted aromatic amines in presence of $Et_3N$and MDC as solvent and corresponding through multi-step reactions. First step involves the reaction of 6-hydroxy-9H-carbazole-3-carboxylic acid (2) obtained from the mixture of p-amino acetophenone and p-benzophenone in the presence of copper iodide in a strong base in acetonitrile at elevated temperature and which also followed 6-hydroxy-9H-carbazole-3-carbonyl chloride can be synthesized from 6-hydroxy-9H-carbazole-3-carboxylic acid and thionyl chloride(Scheme-1).



To explore this scope of novel procedure of the titled derivatives, the condensation reactions of different aromatic amines with compounds.[3] Under optimum reaction conditions, a novel series of carbazole derivatives were synthesized, in all cases, aromatic amines substituted

with either electron-donating or electron withdrawing groups underwent the reaction smoothly and scaffold desired in excellent yields (85%-92%). The reaction products were isolated by simple workup procedure and did not required any further purification steps. The presence of electron donating substituents on the aromatic amines accelerated the reaction rate, whereas electron-releasing substituent retarder the rate of reaction. However, the nature of the substituents did not impact the yield of the product.

The structures of the titled derivatives were characterized by IR, 1HNMR, 13C NMR, mass spectral and elemental analyses. The IR spectrum of compounds (6a-6f) exhibited absorption bands at 3564,3368,3058, 1754, 1678,1589,1541,1506,845cm -1 which corresponds to O-H,N-H, aromatic C-H, CONH, C=O and C=N stretching respectively. Similarly, 1H NMR spectrum of the titled derivatives showed in various aromatic protons appears at δ 8.942 to 6.746 ppm and the methoxy protons showed at δ3.664ppm.The carboxylic protons appear at δ 11.825ppm, The hydroxyl protons appear at δ 9.124ppm,, The NH protons of the derivatives appear at δ 11.196ppm and the amide bond appears at δ 10.036 ppm .The mass spectrum of "6e" showed molecular ion peak at 382.43 (M+2) which is in agreement with the molecular formula $C_{19}H_{13}BrN_2O_2$.

4.2. Antimicrobial activity

All the newly synthesized and procured derivatives were evaluated for anti-micro bacterial and antifungal activity; the results represented to shown in **(Table- I).**

As indicated in Table. I- the majority of the MIC results for the tested compounds showed a potentially good effect against. The compound 6c showed the highest antimicrobial activity and compounds "6c and 6d" exhibited an excellent activity against bacterial strains (Table-I). It reveals that the activity of derivatives 6b and 6c, which bearing electron donor groups and also the 4-position of substituents in aromatic ring. It is also evident that the benzene rings substituted with electron attracting groups such as Cl, Br and NO_2 exhibited better activity than donor substituent such a OMe in 4b or substituted phenyl ring compound such as 6d and 6e compounds Presence of Cl and Br substitution in 4-position in benzene ring resulted in better activity against Mycobacterium than compound 6e which include Cl substitution in 4-position. In of 6-hydroxy-N-phenyl-9H-carbazole-3-carboxamide such as **6a-6f**, showed better anti-mycobacterial activity. Moreover, to assess antimicrobial activity of these derivatives of antifungal activity was also evaluated. A.Ngier and C.albicans are introduced as good to excellent for antifungal activity against test derivatives. Mainly, the tested

derivatives exhibited poor activity against C.albicans, compounds (6a-6e) whereas the compound "6f" exhibited most potent activity against the fungal activity. Which was synthesized from 6-hydroxy-N-(4-nitrophenyl)-9H-carbazole-3-carboxamide can be synthesized by the with substituted 4-Nitro aniline scored the highest antifungal activity.

Table I: Antimicrobial activity screening activity titled compounds (6a-f).

Compound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substill	A. niger	C. albicans
6a	04	06	08	06	06	09
6b	13	15	14	16	08	09
6c	20	21	16	17	09	09
6d	20	21	17	18	10	12
6e	09	11	10	08	17	16
6f	12	13	12	15	08	10
Ciprafloxin	25	25	22	22	NA	NA
Fluconazole	NA	NA	NA	NA	20	20
DMSO	---	----	---	---	---	---

5. CONCLUSION

In conclusion, we have been achieved a convenient protocol for the synthesis 6-hydroxy-N-phenyl-9H-carbazole-3-carboxamide from p-benzoquinone and P-amino benzoic acid. Incorporated moiety in excellent yield and evaluated there *in vitro* anti-bacterial and anti-fungal strains. Our antimicrobial activity evaluated results represented that exciting was observed in compounds in comparison with standard Ciprafloxin and Fluconazole. The majority derivatives are emerging with the most active potent and antimicrobial activity in this study will be further structurally modified towards the discovery of a compound with optimal antimicrobial activity. These results may also provide some significance guidance for the development of new class biological studies.

6. ACKNOWLEDGMENT

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