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DESIGN, SYNTHESIS, AND ANTIBACTERIAL ACTIVITY OF NOVEL AMIDE-COUPLED 6-HYDROXY-N-PHENYL-9H-CARBAZOLE-3-CARBOXAMIDE PROMOTED BY DCC

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ABSTRACT

The study of antimicrobials activity having a unique mode of action is a minimum requirement to solve problems of multi-drug resistance challenges. Here in, we have designed and prepared amide-coupled 6-hydroxy-N-phenyl-9H-carbazole-3-carboxamide (6a-6f) by acid-amine coupling reaction of 6-hydroxy-9H-carbazole-3-carbonyl chloride with substituted aromatic amines in the presence of strong base and dehydrohalogenating such as DCC. The intermediate 6-hydroxy-9H-carbazole-3-carbonyl chloride can be obtained from p-amino benzoic acid with p-benzoquinone in acetonitrile in the presence of a copper acetate in a alkali metal base and clean RBF. The copper acetate and caesium carbonate added in RBF. The synthesized amide-coupled scaffolds were characterized through ^{1}HNMR, ^{13}CNMR, as well as mass spectroscopic techniques. These analogous were evaluated for their antimicrobial against standard drug.

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

1. INTRODUCTION

Amides are one of the most important significant functional groups in organic chemistry s and medicinally chemistry due to their presence in several interesting moieties such as naturally occurring molecules, pharmaceutical agents, peptides, proteins and alkaloids, among others. This literature surveys of the diverse recent approaches to amide synthesis from non-activated carboxylic acids and analogous as well as monocarboxylic compounds, the most innovative procedure and those that is more eco-friendly compared to traditional

methods while mainly focusing on recent improvement during the past two decades. The development of an efficient as well as convenient procedure for the synthesis of amides has been a key goal in synthetic chemistry due their prevalence in synthetic chemistry and the life sciences.[1–10]

A major impact of the modern chemistry is the path of the new chemical reaction successions that supply novel compounds in high yields. Amides are an incredibly broad significant vital group of organic moieties and a variety of functions. The several derivatives of amides represents pharmacological properties viz; anti-inflammatory agents,[11] Antioxidant Activity,[12] anticancer activity,[13] fungicide and antibacterial,[14-17] H1-receptor antagonists.[18] The conventional method of approach for the synthesis of amides coupling is the reaction of carboxylic acids and amines at high temperature. Due to carboxylic acid's poor activity, numbers of procedures for their activation have been reported in the literature. There is no consideration of the aspects of these methods having encouragement yields, by products, costly coupling reagents and difficulty in removal of surplus reagents. Consequently, the growth of a new and non-complicated synthetic method for the preparation of amides has become an interesting challenge.

Ongoing our study, we report synthesis of 6-hydroxy-N-phenyl-9H-carbazole-3-carboxamide based analogous**(6a-6f)** via amide bond formation between 6-hydroxy-9H-carbazole-3-carbonyl chloride and various substituted aromatic amines containing different substituents such as nitro, halogen, methoxy etc. Now, the synthesized amide-coupled 6-hydroxy-N-phenyl-9H-carbazole-3-carboxamide scaffolds from starting material p-amino benzoic acid (1mmol), p-benzoquinone. The scaffolds were evaluated for their antibacterial and antifungal potential. For these derivatives of potential therapeutic, it is an important to estimates plausible molecular weight of desired compounds that can be 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 procured from commercially and they were applied without further purification. The standard procedures were used to follow by dry solvents and reaction mixture were examined by thin-layer chromatography (n-hexane: Ethylacetae) on silica gel plates coated with alumina. The melting points of the titled derivatives were estimated in open capillary tubes and were uncorrected. ^{1}HNMR and ^{13}C-

NMR spectrum were measured titled derivatives on a Bruker 400MHz and 100MHz instrument using $CDCl_3$ as a solvent. The mass spectra of the synthesized derivatives were obtained on a Shimadzu 2010A LCMS spectrometer.

2.1.The general procedure of 6-hydroxy-9H-carbazole-3-carboxylic acid (3)

The mixture of p-amino benzoic acid (1mmol), p-benzoquinone (1.5mmol) dissolved in acetonitrile in a dry and clean RBF. The copper acetate and caesium carbonate added in RBF. The total set up arranged on the magnetic stirrer and was maintained 5hrs at 75^0C. The reaction mixture was monitored by TLC (5:5-Ethyl acetate: n-hexane). After completion of the reaction, catalyst was filtered and the reaction crude with ethyl acetate and washed solution of $NaHCO_3$. The ethyl acetate layer separated kept side and aqueous layer washed with (10mL) after separated. Both of the organic layers combined distilled organic layer. Crude product was separated by columns chromatography and recrystallization from ethanol.

Characterisation

Pale red solid; Yield-85%, M.P-258-260^{0}C; ^{1}HNMR (400MHz, CDCl3) ppm: 11.569 (s, 1H,-COOH), 11.214 (s,1H, NHCO-), 8.942 (s, 1H, -OH), 8.628 (s, 1H, Ar-H), 8.168 (d, J= 8.2 Hz, 1H, Ar-H), 7. 885 (d, J=6.4Hz, 1H, Ar-H), 7.582 (s,1H,Ar-H), 7.312 (d, J= 7.2Hz, 1H, Ar-H), 7.123(d,J=7.0Hz,1H,Ar-H) ;^{13}CNMR (100MHz, $CDCl_3$) ppm: 172.05, 148.71, 138.30,135.65,129.41,124.55,121.67,115.09,113.28,11.96,110.75,and102.60;LCMS(m/z): 226.86(M-H);Molecular formulae: $C_{13}H_9NO_3$;Elementalanalysis:Calculated:C-68.71,H- 3.93, N- 6.16; Obtained: C- 68.65 , H- 3.92 ,N-6.25.

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

Take clean and dry 50mL RBF.25mL methylene dichloride introduced into a RBF and 6-hydroxy-9H-carbazole-3-carboxylic acid (1mol) is dissolved in solvent. The thionyl chloride poured into drop wise with help of dropping funnel in a RBF in 10-20^{0}C. The total arrangement adjusted 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

Brown red solid; Yield-88%,^{1}HNMR(400MHz,$CDCl_3$)δ ppm: 11.458 (s, 1H, NH-indole), 8.910 (s, 1H, -OH), 8.764 (s, 1H, Ar-H), 8. 195 (d, J= 8.0 Hz, 1H, Ar-H), 7. 512 (d, J= 8.0Hz, 1H, Ar-H), 7.496 (s, 1H, Ar-H), 7.284(d, J= 7.2Hz, 1H, Ar-H), 6. 871 (d, J=6.8Hz, 1H, Ar-

H);^{13}CNMR (100MHz, $CDCl_3$) ppm: 168.92, 152.58, 148.47, 139.54, 129.72, 128.47,124.70, 122.58, 115.30, 113.54, 113.41, 103.62; LCMS (m/z):247.87 (M+H);Molecular formulae: $C_{13}H_8ClNO_2$; Elemental analysis: Calculated: C- 63.57, H- 3.29, N- 5.70; Obtained: C- 63.47, H- 3.27 , N- 7.74.

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

Take clean and dry 50mL RBF and 25mL methylene dichloride poured in a RBF and 6-hydroxy-9H-carbazole-3-carbonyl chloride (1.25mol) is dissolved in a solvent and substituted aromatic amines introduced into the above solution and strong base such as triethyl amine is slowly addition to portion wise in the solution. The reaction is continued for 2 hrs. at reflux. The reaction mixture was monitored by the TLC (EtOAc: n-hexane-4:6) after completion of the reaction time, the mixture was cooled under tap water and then neutralized with 2NHCl. The completion of the neutralization, ethyacetate added into the solution and separated the organic layer and washed with water. 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 solid ; Yield-82%, M.P-247-249^{0}C;^{1}HNMR (400MHz, $CDCl_3$) ppm: 11.214 (s, 1H, NH-indole), 10.258 (s, 1H, -CONH), 8.847 (s, 1H, -OH), 8.554(s, 1H, Ar-H), 7.851-7.514 (m ,4H,Ar-H),7.484(s,1H,Ar-H),7.456-7.278(m,3H,Ar-H),7.247-7.014(m,3H,Ar-H);^{13}CNMR (100MHz,$CDCl_3$)ppm:166.84,152.25,139.54,136.07,134.65,129.46,128.92,128.41,127.78, 125.64,122.36,120.54,113.71, 112.47, 111.21, 108.94, 102.87.LCMS (m/z): 301.69(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 compound; Yield-85%,M.P-258-260^{0}C;^{1}HNMR (400MHz, $CDCl_3$) ppm: 11.453 (s, 1H, NH-indole), 10.745 (s, 1H,-CONH-),9.258 (s, 1H, -OH), 8.533 (s, 1H, Ar-H), 8. 136 (d, J= 8.4 Hz, 1H, Ar-H), 7. 554 (d, J= 9.2Hz, 1H, Ar-H),7.524(d, J= 6.4 Hz, 2H, Ar-H), 7.598 (s, 1H, Ar-H), 7.292(d, J= 6.8 Hz, 1H, Ar-H), 7.253-6.951(m,3H Ar-H) , 3.687(s,3H,-OCH_3); ^{13}CNMR (100MHz, $CDCl_3$) ppm: 166.71, 153.85, 147.66, 138.17, 136.68, 129.69, 128.54,126.71, 122.58, 120.64, 116.03, 113.74, 111.71, 110.66,103.77, 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)

Pale brown solid; Yield-87%; ^{1}HNMR (400MHz, $CDCl_3$) ppm: 11.256 (s, 1H, NH-indole), 10.145 (s, 1H,-CONH-), 9.194 (s, 1H, -OH), 8.584 (s, 1H, Ar-H), 8. 164 (d, J= 7.2 Hz, 1H, Ar-H),7.674(d, J= 6.8Hz,1H, Ar-H), 7.507(s,1H Ar-H), 7.467.288(m, 4H, Ar-H);^{13}CNMR(100MHz,$CDCl_3$)ppm:166.01,150.86,139.57,136.65,133.19,131.29,129.06,128.87,128.33,127.54,123.48,120.34,119.55,114.38,113.64,109.41;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- 89%,^{1}HNMR (400MHz, $CDCl_3$) ppm: 11.394 (s, 1H, NH-indole), 10.142 (s, 1H,-CONH-), 9.217 (s, 1H, -OH), 8.647 (s, 1H, Ar-H), 8. 254 (d, J= 8.4 Hz, 1H, Ar-H), 7. 685 (d, J= 8.0 Hz, 1H, Ar-H), 7.654-7.458(m, 4H, Ar-H), 7.427 (s, 1H, Ar-H), 7.251-7.014 (m, 2H, Ar-H); ^{13}CNMR (100MHz, $CDCl_3$) ppm: 167.99,151.68, 144.54, 138.94, 131.54, 129.27, 128.16, 126.70, 126.03, 124.22, 122.32, 120.07, 114.03, 112.07,110.78, 103.66.LCMS (m/z): 382.24 (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 solid; Yield-85%, ^{1}HNMR (400MHz, $CDCl_3$) ppm: 11.572 (s, 1H, NH-indole), 10.346 (s, 1H,-CONH-), 9.246 (s, 1H, -OH), 8.423 (s, 1H, Ar-H), 8. 176 (d, J= 7.2 Hz, 1H, Ar-H),7.955(d,J= 8.4 Hz, 1H, Ar-H), 7.824(d, J= 6.8 Hz, 1H, Ar-H), 7.587(d,J=6.2Hz,1H,Ar-H);^{13}CNMR(100MHz,$CDCl_3$)ppm:169.07,152.23,142.02,141.36,139.48,137.65,129.49,129.11,128.92,128.02,127.64,123.74,120.34,113.57,111.76,110.68,109.74,101.90.LCMS(m/z): 347.26(M+);Moleculaformulae:$C_{19}H_{13}lN_3O_4$; 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-88; ^{1}HNMR (400MHz, $CDCl_3$) ppm: 11.344 (s, 1H, NH-indole), 10.587 (s, 1H,-CONH-), 9.254 (s, 1H, -OH), 8.521 (s, 1H, Ar-H), 8. 134 (d, J= 8.0 Hz, 1H, Ar-H), 7. 940(d,J=8.8Hz,1H,Ar-H),7.741-7.324(m,3H,Ar-H),7.318-7.274(m,3H,Ar-H);^{13}CNMR(100 MHz,$CDCl_3$)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):309.55(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-9.19.

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

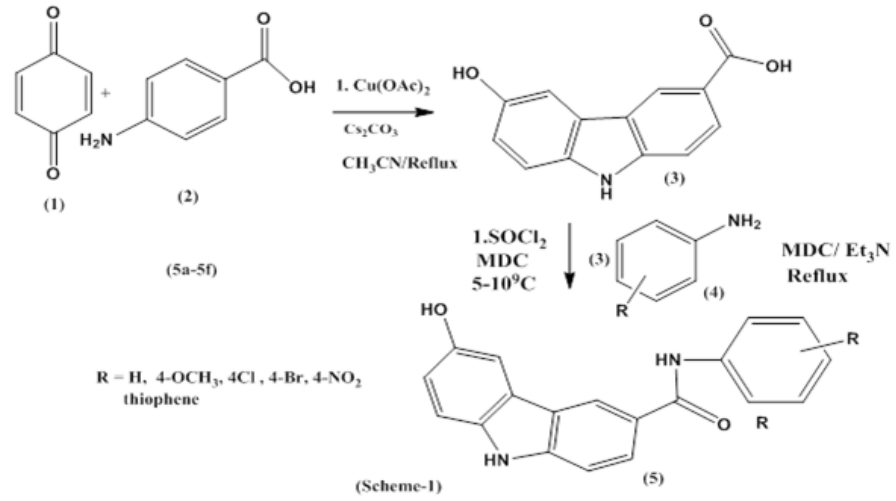
In vitro antifungal screening against A.niger and Candida albicans was used as test strain. The tested derivatives were dissolved in dimethyl sulfoxide (DMSO) and prepare to concentration of 10 mg/mL. Antifungal activity of these compounds was performed by broth micro dilution method. The absorbance 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

The present investigation of the synthesis of novel analogous a series of 6-hydroxy-N-phenyl-9H-carbazole-3-carboxamide (6a6-f).These derivatives were prepared from 6-hydroxy-9H-

carbazole-3-carbonyl chloride and aromatic amines in presence of strong base $Et_3N$and MDC as solvent and followed by multi-step reactions. First step involves the reaction of 6-hydroxy-9H-carbazole-3-carboxylic acid (2) synthesized from the mixture of p-amino acetophenone and p-benzophenone in the presence of copper acetate in a strong base such as Cs_2CO_3 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).



(Scheme-1)

To explore this scope of novel method of the desired derivatives, the condensation reactions of the various 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 required compounds in excellent yields (83%-902%). The reaction was isolated by simple workup procedure and did not follow by any required and further purification steps. The presence of electron releasing substituents on the aromatic amines enhanced the rate of reaction while electron-withdrawing substituent retarder the rate of reaction. However, the nature of the substituents dependent and impact the yield of the product.

The structures of the titled derivatives were characterized by ^{1}HNMR, ^{13}C NMR, mass spectral and elemental analyses, 1H NMR spectrum of the titled derivatives showed in various aromatic protons appears at δ 8.842 to 6.987 ppm and the methoxy protons showed at δ3.714ppm.The carboxylic protons appear at δ 11.754ppm, The hydroxyl protons appear at δ 9.224ppm,, The NH protons of the derivatives appear at δ 11.496ppm and the amide bond

appears at δ 10.236 ppm. The mass spectrum of "6e" showed molecular ion peak at 382.55 (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 analogous were screened 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 derivatives exhibited a potentially high effect against bacterial as well as fungal strains. The compound 6c showed the highest antimicrobial activity and compounds "6c and 6d" exhibited an excellent activity against bacterial strains (Table-I). The results was reveals that the activity of derivatives 6b and 6c, which having electron releasing groups and also the 4-position of substituents in benzene nucleus. It is also be represented that the benzene rings substituted with electron attracting groups such as Cl, Br and NO_2 which was exhibited excellent activity than releasing 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 good 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 analogous of antifungal activity was also examined. A.Ngier and C.albicans are showed 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-6f).

Compound Code	*Zone of inhibition in (mm)					
	Bacteria				Fungi	
	S.aureus	E.coli	S. typhi	B.substill	A. niger	C. albicans
6a	05	08	07	08	05	09
6b	13	15	14	16	08	09
6c	21	22	19	20	09	09
6d	20	21	21	19	10	12
6e	09	10	11	09	16	17
6f	13	14	14	16	09	11
Ciprafloxin	25	25	22	22	NA	NA
Fluconazole	NA	NA	NA	NA	20	20
DMSO	---	----	---	---	---	---

5. CONCLUSION

In conclusion, we have been attracted and attention of the achieved a convenient protocol for the synthesis 6-hydroxy-N-phenyl-9H-carbazole-3-carboxamide from p-benzoquinone and substituted P-amino benzoic acid. The target moiety was exhibited in an excellent yield and examined there *in vitro* anti-bacterial and anti-fungal strains. Our antimicrobial activity evaluation results represented that exciting was observed in comparison with standard Ciprafloxin and Fluconazole. The majority of analogous 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 improvement of new class biological studies.

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