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RESEARCH ARTICLE

AN EFFICIENT SYNTHESIS OF (E)-6-(1-(PHENYLIMINO) ETHYL)-9H-CARBAZOL-3-OLDERIVATIVES AND EVALUATION OF THEIR ANTIMICROBIAL ACTIVITIES

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ABSTRACT

The synthesis of a number of Schiff bases of (E)-6-(1-(phenyldiamine) ethyl)-9H-carbazol-3-ol derivatives was thoroughly studied, and biological properties were also investigated. P-benzoquinone with 4-amino acetophenone in the presence of copper iodide in CH_3CN with strong bases like Cs2CO3 at reflux can be obtained from substituted aromatic amines with hetero aromatic amines using compound (3) in the presence of Bronsted acid methane sulfonic acid in ethanol as solvent. Spectroscopic techniques like mass spectral analysis and ^{1}H NMR and ^{13}CNMR were used to confirm all the produced analogues. Elemental analysis was used to examine the compounds' structures. Two gram (+Ve) and two gram (-Ve) bacterial strains were used to evaluate each derivative.

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INTRODUCTION

Schiff bases are the condensation products of primary amines and carbonyl compounds, either aldehydes or ketones. Hugo Schiff, a German scientist who won the Nobel Prize, made the discovery in 1864. Imines are organic substances that have an azomethine (–HC=N-) group in their structure. Thus, these substances have a wide-ranging and important significance in the drug moiety manufacturing process. In terms of structure and properties, the azomethine group (C=N) is between the groups of NH_2 and C=O. All of these groups have two electrons in the π orbital, and these electrons are responsible for some of the unique characteristics of compounds that contain these groups. The produced imine can coordinate with heteroatoms like nitrogen that have nonbonding electrons and metal ions. By regulating their performance and a variety of catalytic conversions, the Schiff base can really stabilize many of the oxidation states of metals. In the vast fields of synthetic organic chemistry and medicinal science, schiff base is a significant molecule. It has been determined that the imine linkage is a highly bioactive and medically significant moiety. Because of its remarkable complex metric role and pharmacological applications, azomethine and its derivatives have been studied *(*3, 4*)*. As a result, it plays a significant and prominent role in major areas of biological activities *(*5-7*)*, including antimicrobial *(*8–18*)*, anticancer *(*19–21*)*, anticonvulsant *(*22, 23*)*, anti-HIV *(*24*)*, anti-helminthic *(*25*)*, antiviral *(*26*)*, anti-malarial *(*27, 28*)*, anti-inflammatory *(*29–31*)*, and anti-oxidant *(*32–33*)*. Our ongoing research focuses on the synthesis of Schiff's base using an intermediate like cabriole, the efficient and flawless synthesis of (E)-6-(1-(phenyldiamine) ethyl)-9H-carbazol-3-ol derivatives, and the assessment of their antibacterial properties.

METHODS AND MATERIALS

Experimental: Merck and Aldrich were the suppliers of all starting materials, solvents, reagents, and analytical grade. The uncorrected melting points of the recently synthesized analog were determined using electro Agarwal thermal equipment in open capillary tubes. Using n-hexane/EtOAc (2:1) as an eluent, thin layer chromatography on silica gel coated aluminum plate chromatography (TLC) was used to assess the compounds' purity. The compounds' 1H NMR and 13CNMR spectra were recorded on a Brucker AMX 400 MHz spectrometer using

CDCl3 as a solvent and tetra methyl silane (TMS) as an internal standard. Coupling constants and chemical shifts are expressed in Hz and δ, respectively.

General procedure of 1-(6-hydroxy-9H-carbazol-3-yl) ethan-1-one: In a dry and clean RBF, a combination of p-amino acetophenone (1.110 mmol) and p-benzoquinone (1.0 mmol) was mixed in 25 mL of toluene. Caesium carbonate and copper acetate were added to an RBF. The entire setup was placed on the magnetic stirrer and kept at 1000C for six hours. TLC was used to identify the reaction mixture (4:6-Ethyl acetate: n-hexane).The catalyst was filtered once the reaction was finished, and the reaction liquid was then added to a beaker along with ethyl acetate and a cleaned sodium bicarbonate solution. After the separation of the organic layer, the aqueous layer was cleaned with 10 milliliters. Together, the two organic layers evaporated under vacuum. Column chromatography and recrystallization from ethanol were used to isolate the crude product.

Palebrownsolid; Yeild-90%;m.p-222-224^{0}C;^{1}HNMR(400MHz, $CDCl_3$) δppm:10.624 (s,1H,N-H:indole), 9.452(s,1H,-OH),8.218 (s,1H,Ar-H), 8.048-7.884 (m,2H,Ar-H),7.441(s,1H,Ar-H),7. 404-7.205 (m,3H,Ar-H), 1.595(s,3H,-CH_3);^{13}CNMR (100MHz, CDC l3) δppm: 167.58,1 51.77,145.28,1 38.58,128.98, 128. 14,127.55,126.54 ,123.26,120. 08,115.06,11 1.81,109.54,10 4.64,20.84;LC MS(m/z):225.41(M-2);Molecula rformule:$C_{14}H_{11}NO_2$. Elemental analysis: calculated:C-74.64,H-4.91,N-6.23;Obtaine d:C-74.55 ,H-4.90,N-6.32.

General procedures of (E)-6-(1-(phenylimino) ethyl)-9H-carbazol-3-ol (5a-f):

General procedures for synthesis of Schiff base compounds: Using a dropping funnel, the combination of 1-(6-hydroxy-9H-carbazol-3-yl) ethan-1-one (1 mol) and trifluoroacetic acid (3 mL) was added gradually. After two hours at room temperature, one mole of substituted aromatic amines was added to the mixture, which was then agitated and cooked to 60 degrees Celsius under reflux conditions. Thin layer chromatography (TLC) was used to monitor the reaction's development. Cold water was added to the mixture once the reaction was finished. Following the formation of crystalline crystals at the beaker's bottom, they were filtered. The solid product was then dried in a desiccator at room temperature after being cleaned with water, ethanol, and n-hexane. Good yields of the pure derivatives were achieved.

E)-6-(1-(phenylimino) ethyl)-9H-carbazol-3-ol (5a): Redsolid; Yeild-87%; m.p-212-214^{0}C^1 HNMR (400MHz,$CDCl_3$) δppm): 10.612 (s,1H,N-H:indole), 9.257 (s,1H,-OH), 8.525(s,1H,Ar-H),8.294-8.015 (m,2H,Ar-H),7.514 (s,1H,Ar-H),7.418-7.284(m,3H,Ar-H),7.214-6.965 (m,3H,Ar-H),1.845(s,3H,-CH3);^{13}CNMR (100MHz,$CDCl_3$) δppm:165.58, 151.57, 143.09,136.12, 129.32,128.85,128.24,125.44,122.58,120.07,113.36,112.61,11 1.54,108.07, 102.54,19.42.LCMS (m/z):317.58(M+H); Molecularformule: $C_{20}H_{16}N_2O_2$. Elementalanalysis: Calculated:C-75.93, H-5.10,N-8.85; Obtained:C-75.86,H-5.08,N-8.93.

(E)-6-(1-((4-metoxyphenyl) imino) ethyl)-9H-carbazol-3-ol (5b): Paleredsolid;Yeild-91%;m.p-222-224^0 C;^{1}HNMR(400MHz,$CDCl_3$) δppm):10.158 (s,1H,N-H, indole),9.314 (s,1H,-OH),8.412 (s,1H,Ar-H),8.054 (d,J=8.6Hz,1H,Ar-H), 7.948 (d,J=8.4 Hz,1H,Ar-H),7.816 (d,J=7.4Hz,1H,Ar-H),7.524 (s,1H,Ar-H);7.486-7.346 (m,2H, Ar-H),7.254-6.960 (m,4H,Ar-H),1.214 (s,3H,-CH_3);^{13}CNMR(100MHz, $CDCl_3$)δppm:166.73, 157.94,151.74,1 49.38,14 2.11,136.88,131.24,128.8 4,126.74,121.76,1 18.95,116.55,114.70, 113.84,112.64,11 0.43,108.38,107.74,102.69, 21.77.LCMS(m/z):301.75(M+H); Molecularformule: $C_{20}H_{16}N_2O$; Elemental analysis: Calculated: C-79.91,H-5.38,N-9.36;Obtained:C-79.85,H-5.34,N-9.42.

(E)-6-(1-(p-tolyl imino) ethyl)-9H-carbazol-3-ol (5c): Pale milky white solid ;Yeild-90%; M.p-234-237^{0}C;^{1}HNMR(400MHz,$CDCl_3$)δppm:10.317 (s,1H,N-H, indole), 9.257(s,1H,-OH),8.123(s,1H,Ar-H), 7.911-7.745 (m,2H,Ar-H),7.741 (s,1H,Ar-H),7.564 -7.410 (m,2H,Ar-H),7.387-7.084 (m,4H,Ar-H),1.564(s,3H,-CH_3);^{13}CNMR (100MHz,$CDCl_3$) δppm:167.58,152.23,147. 87,142.46, 138.55,135 .52,129.82,128 .96,127.54,126 .33,124.28,116 .58,115.78,113.69,112.04,110.22,108.80,104.57,20.54,19.12; LCMS(m/z):31 512(M+H);Molecularformule:$C_{21}H_{18}N_2O$. Elemental Analaysis: Calculated:C-80.23,H-5.77,N-8.91; Obtained:C-80.15,H-5.75,N-8.98.

(E)-6-(1-((4-hydroxyphenyl) imino) ethyl)-9H-carbazol-3-ol (5d): Brown solid;Yeild-92%;M.p-235-237^{0}C;^{1}HNMR (400MHz,$CDCl_3$) δppm:10.539 (s,1H,N-H, indole),9.348 (s,1H,-OH), 8.958 (s,1H,-OH),8.567(s,1H,Ar-H),8.234 (d,J=8.6Hz, 1H,Ar-H),7.856 (d,J=8.8Hz,1H,Ar-H),7.712(d,J=6.8Hz,1H,Ar-H),7.514 (s,1H,Ar-H);7.446-7.286(m,2H,Ar-H),7.214-6.914 (m,4H,Ar-H),1.275(s,3H,-CH_3);^{13} CNMR(100MHz,$CDCl_3$) δppm:166.74, 154.91,151.76, 149.57,142.68,139.35,131.24,128.91,126.74,123.68,118.94,11 6.87,114.78,113.84,111.73,110.05,109.49 ,106.75,103.69,21.77; LCMS(m/z):301.79 (M+H); Molecularformula: $C_{20}H_{16}N_2O$. Elementalanalysis: Calculated:C-79.94,H-5.36,N-9.29;Obtained:C-79.88,H-5.34,N-9.36.

E)-6-(1-((4-chlorophenyl) imino) ethyl)-9H-carbazol-3-ol (5e): Pale Redcompound;Yield-88%;m.p-241-243^{0}C;^{1}HNMR(400MHz,$CDCl_3$)δppm:10.828(s,1H,N-H, indole),9.619(s,1H,-OH),8.687(s,1H,Ar-H),8.242-8.004(m,2H,Ar-H), 7.886(s,1H,Ar-H),7.618-7.307(m,3H,Ar-H),7.207-6.899 (m,3H,Ar-H),1.657(s,3H,-CH_3);^{13}CNMR (100MHz,$CDCl_3$) δppm:168.57,154.87, 144.87,138.14, 29.27,128.89, 128.28,127.70,124.95, 121.26,115.47, 112.64,110.55,109.65,103.54, 21.87.LCMS(m/z):317.88 (M+H);Molecularformule:$C_{20}H_{16}ClN_2O_2$.Elemental analysis: Calculated: C-75.94,H-5.11,N-8.84; Obtained: C-75.88,H-5.09,N-8.94.

(E)-6-(1-((4-Bromophenyl) imino) ethyl)-9H-carbazol-3-ol (5f): Red compound ; Yields -89%; M.p-240-242^{0}C;^{1}HNMR (400MHz,$CDCl_3$)δppm:10.907 (s,1H,N-H, indole),9.587 (s,1H,-OH),8.489 (s,1H,Ar-H),8.042-7.884(m,2H,Ar-H), 7.857 (s,1H,Ar-H), 7.556-7.287(m,3H,Ar-H),7.224-6.923(m,3H,Ar-H),1.065(s,3H,-CH_3);^{13} CNMR(100MHz, $CDCl_3$)δppm: 169.57,155.87,144.54,138.08,129.77,128.74,128.26,126.71,12 4.95, 122.66, 116.47,112.64,110.55,107.71,102.54, 21.41.LCMS(m/z):394.37(M+H); Molecularformule: $C_{20}H_{16}BrN_2O_2$.. Elemental Analaysis: Calculated:C-75.93,H-5.10,N-8.85;Obtained:C-75.86,H-5.08,N-8.93.

(E)-6-(1-((4-nitrophenyl) imino) ethyl)-9H-carbazol-3-ol (5g): Yellowsolid;Yeild-87%;m.p-250-252^{0}C;1HNMR(400MHz,$CDCl_3$) δppm):10.902(s,1H,N-H:indole),9.247 (s,1H,-OH),8.547 (s,1H,Ar-H),8.182-7.712(m,4H,Ar-H), 7.413-7.284(m,2H,Ar-H),7.039-6.874(m,2H,Ar-H), 1.012(s,3H,-CH_3);^{13}CNMR (100MHz,$CDCl_3$) δppm:168.55,151.65 ,141.78,137.65,136.74,135.84,129. 33,128.57,127.04,125.72,122.81,113.07,112.74,111.44,110 .13,108.70,101.06,18.04.LCMS(m/z):346.07(M+H); Molecularformule:$C_{20}H_{15}N_3O_3$. Elementalanalysis: Calculated:C-69.56,H-4.38,N-12.17;Obtained:C-69.48,H-4.36,N-12.24.

(E)-6-(1-(thiophen-2-ylimino) ethyl)-9H-carbazol-3-ol (5h): Paleyellowsolid;Yeild-85%;m.p-230-232^{0}C;^{1}HNMR(400MHz,$CDCl_3$) δppm):10.864(s,1H,N-H:indole),9.145(s,1H,-OH),8.446 (s,1H,Ar-H),8.055-7.903(m,2H,Ar-H), 7.691-7.470(m,2H,Th-H),7.433(s,1H,Ar-H),7.413-7.285 (m,2H,Ar-H),0.987(s,3H,-CH_3);^{13}CNMR (100MHz,$CDCl_3$) δppm:167.28,151. 38,140.54,136.55,129.55,128.76,128.07,127 .55,124.15,120.78,114.76,112.40,112.11,111.08,108.76,101.62,18.66.LCMS(m/z):306.52(M+); Molecularformule: $C_{18}H_{14}N_2OS$; Elementalanalysis: Calculated:C-70.56,H-4.61,N-9.14;Obtained:C-70.48,H-4.60,N-9.22.

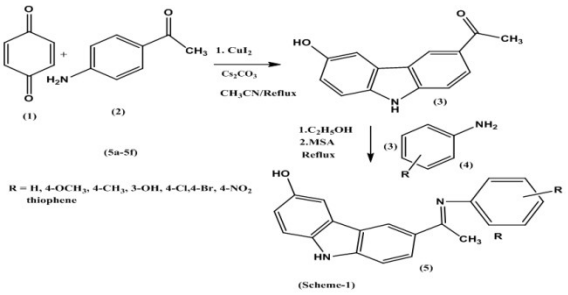
Antimicrobial Evaluation:

Anti-bacterial activity: Four pathogenic bacterial strains are tested for the intended synthesized compounds' in vitro antibacterial properties. P. aeruginosa and E. coli were the gram-negative bacteria that were examined. S. aureus and B. substill were the gram-positive bacteria that were screened. Streptomycin was utilized as a standard and the target compounds were used at concentrations of 250 µg/mL and 500 µg/mL using DMSO as a solvent in a 10 µg/mL disc. The remaining substances were discovered to have moderate activity against the pathogen under test.

Antifungal assay: Sterile molten potato dextrose agar (PDA) medium was inoculated with 50 lL of fungal spore suspension aseptically and maintained at 45^{0}Ctemperature. The inoculated medium was mixed well and poured immediately in sterilized petriplates. Then five wells of 6 mm diameter were punched using sterile borer and filled with 100 lg/mL of test compounds (6a-l) as well as sterile DMSO 100% as negative control. Plates were incubated for 24 h at 37^{0}C. Antifungal activity was determined by measuring the zone of inhibition. The zones produced by the test compounds were compared with the "ketoconazole".

RESULTS AND DISCUSSION

Chemistry: The titled derivatives were obtained in two steps (Scheme -1). At first, Synthesis of 1-(6-hydroxy-9H-carbazol-3-yl) ethan-1-one was prepared, according to a method with a two-component reaction comprising of P-amino acetophenone and P-benzoquinone in acetonitrile as solvent using copper iodide with strong base such as Cs_2CO_3 at75^{0}C .The reaction of P-benzoquinone and P-amino acetophenone were employed as a template to optimize the reaction conditions (Scheme-I). Therefore, a mixture of P-amino acetophenone (1mol), and P-benzoquinone (1mol) acetonitrile was stirred for suitable time as represented by TLC using the various amounts of catalyst at



(Scheme-1)

the end of reaction, the cyclisation between P-amino acetophenone, and P-benzoquinone followed with addition catalyst resulted in only one product called (3). For optimization of the amount of catalyst needed for this reaction, of 1-(6-hydroxy-9H-carbazol-3-yl) ethan-1-one was applied as a model analogous and different amounts of catalyst were tested under the same conditions. It was found that 5 mol% of catalyst was enough for a desired yield of the product (Table -1). On the other hand, an amount of catalyst more than 5 mol% did not development the yield of required product. To show thatcopper iodide is an efficient catalyst, these two components› reaction was accomplished in the absence of catalyst at room temperature for12 h. This reaction just produced the product of cyclisation between components (1) and (2). The efficiency of the reaction is mainly affected by the amount of the catalyst (Table 1).The optimal amount of the catalyst was 3 mol% (entry3); the higher amount of the catalyst did not noticeably increase yield (entry 4).

Table-1. Screening of amount catalyst in the formation of compound 3

Entry	(Catalyst mol %)	Time (min)	Yield (%)
1	1mol	120	59
2	2mol	120	62
3	3mol	120	85
4	4mol	120	85

After synthesis of 1-(6-hydroxy-9H-carbazol-3-yl) ethan-1-one, their schiff base derivatives (5a-j) were prepared by the condensation reaction between compound (3) and the substituted amines in ethanol with trifluorocetic acid under reflux conditions. All reactions improved corresponding Schiff-bases (5a–j) in excellent yield the results were summarized in Table 3.

Table II. Optimization of the Various catalystpreparation of derivatives (5b)

Entry	Various catalyst	Time (min)	Yield (%)
1	$CuCl_2$	180	49
2	Cu $(OAc)_2$	180	74
3	Copper triflate	180	62
4	Copper Iodide	180	92

After synthesis of 1-(6-hydroxy-9H-carbazol-3-yl) ethan-1-one, their Schiff base analogous**(5a-5h)** were prepared by the condensation reaction between compound (3) and the substitutedaromatic amines in ethanol with methane sulfonic acid under reflux conditions. All reactions produced corresponding Schiff-bases (5a–5h) in good yield; the results were summarized in Table 3. The structures of the desired compounds were constructed on the basis of characterizedby ^{1}HNMR, ^{13}C NMR, mass spectral and elemental analyses. The proton NMR evidences of corresponds to O-H,N-H, aromatic C-H, CONH, C=O and C=N stretching respectively. Similarly,

^{1}HNMR spectrum of the required compounds showed in various aromatic protons appears at δ 8.456 to 6.713 ppm, The hydroxyl protons appear at δ 9.515ppm, The NH protons of the derivatives appear at δ 10.917 ppm and methyl protons appear at 1. 748ppm.The mass spectrum of "5e" showed molecular ion peak at 317.37 (M+H) which is in agreement with the molecular formula $C_{20}H_{16}ClN_2O_2$.

Antibacterial activity: The in vitro antibacterial activity of the newly synthesized derivatives (5a-5f) was compared with standard" Streptomycin'' as collected in (Table-IV). .As indicated in Table-IV, most of the synthesized derivatives generally exhibited potent activity against all the tested bacterial strains. Compound "5c and 5e" showed excellent antibacterial activity against gram-positive bacterial strains viz; E.coli, P. aeruginosa and gram-negative bacterial strains viz; B.Subtilis, and Staphylococcus aureus. The derivatives "5b and5d" showed moderate active potent against bacterial strains. The compounds"5a" showed low activity against bacterial strains. These results reveals that the compounds having electron releasing groups showed good activity than the compounds having electron withdrawing groups.

Table III.Antibacterial activity of the newly synthesized compounds (5a-h)

Compound	Anti-Bacterial Activity			
	Gram(+ve) bacteria		Gram(-ve) bacteria	
	E. c.	P.a.	B. s.	S.a.
5a	08	10	08	07
5b	17	14	14	13
5c	18	17	17	18
5d	21	20	22	21
5e	21	22	21	20
5f	20	21	19	20
5g	14	14	13	10
5h	19	20	18	18
Streptomycin	25	25	25	25
DMSO				

Table IV. Antifungal activity of the synthesized compounds (5a-f):

Entry	**Antifungals activity**		
	Aspergillus Niger	**Candida albicans**	Aspergillusfavus
5a	04	07	08
5b	13	14	16
5c	12	10	10
5d	19	13	13
5e	19	16	17
5f	18	16	17
5g	19	20	20
5h	16	18	18
Ketonozole	22	22	22
DMSO			

Zones of inhibition (mm)a of compounds against tested bacterial strains Streptomycin is used as standard. a 100 lg/mL of compound in each well.Values are average of three readings.

Antifungal activity: The in vitro antifungal activity of the newly synthesized derivatives (5a-5f) was compared with standard drug" Ketonozole.'' as collected in (Table-IV). The in vitro antifungal activity of the newly synthesized derivatives (5a-5fl) was studied against A.Ngier and C.albicans.. Compounds 5d and 5f showed significant activity against "A. Ngier" than the fungal strain "C. albicans". 5b and5d were found to be moderately active against tested fungal strain. From the results it is evident that most of the compounds showed significant activity and few are moderately active as shown in Table-.V. The compound 5g, and 5h exhibited the highest potent active against Aspergillusfavus. The compound"5a", exhibited lowest values The remaining derivatives showed moderate potent activities against Aspergillusfavus. These results evidences that the compounds possess electron donating groups exhibited good activity than the compounds possess electron attracting groups.

Table-IV:Antifungal activity of the synthesized compounds (5a-f): Zones of inhibition (mm)a of compounds (5a–h) against tested fungal strains: Values are the average of three readings. Ketoconazole was used as standard. a 100 lg/mL of compound in each well.

CONCLUSION

A convenient route synthesis of trifluorocetic acid from readily available bulk chemicals has been reportedand the full scope of its application in direct imines reactions has been explored. A broad range of ketone and substituted amines containing varying functionalities can be successfully used in methane sulphonic acid in ethanol mediatedanimation reactions, and the pure Schiff's base products can be isolated following an operationally simple solid phase workup procedure using commercially available resins, avoiding the required for aqueous workup or chromatographic purification.

AKOWNLDEMENT

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