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Synthesis and characterization of novel isoxazolyl and pyrazolyl 2, 3, 4, 9 tetrahydro-1H-carbazoles and their antimicrobial studies

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ABSTRACT

A new family of Isoxazolyl 2,3,4,9 -tetrahydro-1H-carbazoles (3a-g) and Pyrazolyl 2,3,4,9-tetrahydro -1H-carbazoles(4a-g) were individually derived using 2,3,4,9- tetrahydro-1H-carbazolyl chalcones(2a-g) by cyclization with hydroxylamine sulfate and hydrazine hydrate respectively. 2,3,4,9 tetrahydro-1H-carbazolyl chalcones were derived from 2,3,4,9- tetrahydro-1H-carbazole by acetylation and followed by aldol condensation .These products were characterized by IR, NMR, MASS spectra and by elemental analysis . All the end products were Screened for antibacterial and antifungal activities.

KEYWORDS

Isoxazolyl 2,3,4,9-tetrahydrocarbazole;
Pyrazolyl 2,3,4,9-tetrahydrocarbazole;
Aldol condensation;
Antibacterial activity;
Antifungal activity.

INTRODUCTION

Carbazole skeleton bearing natural products fused with some other heterocyclic rings have drawn significant attention due to excellent pharmacological activities of several of their analogues. Numerous total syntheses of these natural compounds as well as structural modifications for annulating various heterocyclic systems to carbazole[1-4] have been accomplished.

There are numerous evidences illustrating the fused ring at imine carbazoles have pronounced effect upon pharmacological studies[5,6]. Ondasetron, a carbon linked imidazole derivative of tetrahydrocarbazoles was reported as a highly potent 5 HT3 antagonist and has been used as the radioligand [3H] GR67330 in binding experiments. As per our knowledge, the pyrazoles or isoxazoles fused at the 1st position of tetrahydrocar bazoles are not yet derived. The pyrazole ring system plays an important role in many biological process and used as therapeutic agents[7-9]. Similarly the Isoxazole moiety also has an excellent track record in the medicinal field . More recently, pettit and coworkers isolated the two oxazolyl indoles viz., labradorin 1 and labradorin 2 from pseudomonas syringae, which were found to be potent inhibitors against human cancer cells. The oxazole subunits in natural products are also reported to have potential biological activity against several of their representatives[10-11]. Carbazole derivatives exhibit anti-tumour[12-13], anti-microbial[14] activities. The wider therapeutic applications of fused heterocycles with the carbazole moiety promoted us to synthesize some novel pyrazolyl and Isoxazolyl 1,2,3,4- tertahydocarbazole.

TABLE 1: Antibacterial activity of compounds (3a-g) and (4a-g) (zone inhibition in mm)

Compd.	*B.cereus*	*B.subtilis*	*S.mutans*	*S.aureus*	*S.epidermidus*	*M.luteus*	*E.coli*	*K.pneumoniae*	*P.aeruginosa.*
(3a)	17	19	16	19	18	18	15	14	16
(3b)	22	25	20	24	25	23	20	19	20
(3c)	24	26	23	25	26	25	22	20	23
(3d)	25	28	26	27	28	25	25	23	25
(3e)	29	30	28	29	30	27	26	29	27
(3f)	22	21	23	26	23	24	22	19	22
(3g)	18	20	18	19	19	20	15	13	17
(4a)	16	17	15	17	19	16	16	14	17
(4b)	19	18	16	18	21	20	21	15	18
(4c)	21	20	18	21	24	23	22	20	23
(4d)	22	27	24	23	26	26	25	21	17
(4e)	29	28	28	29	30	26	27	29	28
(4f)	20	26	20	24	25	24	20	19	23
(4g)	24	23	22	20	21	26	24	21	24
Ref. Std	30	31	28	29	30	28	28	29	29

DMF- Negative control : Referent standard Ciprofloxacin

TABLE 2: Antifungal activity of the compounds (3a-g) and (4a-g) (zone inhibition in mm)

Compd.	*A.nigar*	*C.albicans*	*F.oxysporum*	*A.macrospora*
(3a)	16	18	17	14
(3b)	23	22	20	24
(3c)	25	23	30	28
(3d)	27	25	29	27
(3e)	21	20	19	15
(3f)	18	19	17	18
(3g)	11	10	12	14
(4a)	15	17	16	14
(4b)	22	21	22	20
(4c)	23	22	20	22
(4d)	25	23	19	22
(4e)	22	22	20	18
(4f)	17	17	19	20
(4g)	9	11	14	13
Ref.Std	28	30	30	28

DMF-negative control : Referent Standard ;Ketoconazole

Antimicrobial studies

Newly synthesized compounds **(3a-g)** and **(4a-g)** were screened for their in vitro antibacterial activity against *Bacillus cereus, Bacillus subtilis, Streptococci mutans,Staphylococcus aureus,Staphylococcus epidermidus, Micrococcus luteus, Escherichia coli, Klebsiella pneumoniae and pseudomonas aeruginosa* at concentration of 25µg using ciprofloxacin as standard and antifungal activity against *Aspergillus niger, Candida albicans , Altenaria macrospora* and *Fusarium oxysporum* at concentration of 25 µg using ketoconazole as standard . DMF was used as solvent control, nutrient agar was used as culture medium and method employed was cup plate method[15-16]. The zones of inhibition formed were measured in mm and are shown in TABLES 1 and 2 respectively to antibacterial and antifungal activities.

EXPERIMENTAL

General

All melting points are uncorrected .TLC analysis were done on glass plates coated with silicagel-G and spotting was done using iodine. IR (KBr) spectra were recorded on Jasco FT-IR 5300 spectrometer. ^{1}H and ^{13}C NMR spectra were in $CDCl_3$ using jeol GSX 400 (400MHz) and Jeol ECA500 (500 MHz) NMR spectrometer. Mass spectra were recorded using Joel GC mate and MAL-DI-TOF LD. Column chromatography was performed using silica gel (100-200mesh).

General procedure for the preparation of 2, 3, 4, 9-tetrahydrocarbazolyl chalcones (2a-g)

A mixture of acetyl 2, 3, 4, 9 tetrahydro1H-carbazole (3 mmol) and a series of substituted aryl aldehydes (3.6mmol) in ethanol was treated with four percentage of alc. KOH (1.5 equiv). The mixture was stirred for 6 hours at room temperature and the reaction mixture was neutralized by acetic acid. .The residue was filtered off, washed with water and crystallized from ethanol to give **(2a-g)** (SCHEME 1).

(2a) 2,3,4,9-tetrahydro-1H-carbazol-1-yl-3-(phenyl) prop-2-en-1-one

IR (KBr) :3440,1655 cm^{-1} ;1H NMR: δ 1.47-1.52 (m,2H), 1.89(q, 2H), 2.74(t,2H), 3.1 (m, 1H), 7.0-7.12 (m, 5H),7.26-7.45 (m, 4H), 7.45-7.47 (d, 2H, J=9 Hz, vinylic hydrogen), 7.68(b s, 1H, NH).^{13}CNMR: δ 21.2, 25.9, 50.1, 108.3, 111.1, 119.0, 120.1, 126.3, 126.4, 127.4, 128.7, 135.2, 136.2, 142.9, 197.6

MS(EI):m/z301.15 [M.$^+$]; yield : 57%;mp:76^{0}C ;C_{21} H_{19}NO Anal.Calcd.: C,83.69; H,6.25; N,4.65;O, 5.31. Found; C,83.72;H,6.35;N,4.66;O,5.40;

(2b) 2, 3, 4, 9-tetrahydro-1H-carbazol-1-yl-3-(4-tolyl)prop-2-en-1-one

IR (KBr) :3443,1658 cm^{-1};^{1}H NMR: δ1.49-1.56 (m,2H), 1.88(q, 2H), 2.53(s,3H), 2.73 (t,2H), 3.12 (m, 1H), 7.0-7.14 (m, 4H),7.25 -7.43 (m, 4H), 7.45-7.48 (d, 2H, J = 9 Hz, vinylic hydrogen), 7.69(b s, 1H, NH). ^{13}CNMR: δ 21.4, 24.3, 25.2, 50.4, 108.6, 111.3, 119.2, 120.4, 122.2, 126.2, 126.4, 127.3, 129.0, 131.0, 132.2, 136.2,137.6,142.8 , 197.6.MS (EI): m/z315.17 [M.$^+$]; yield :88%;mp:76^{0}C ;C_{22} H_{21}NO Anal. Calcd. C,83.78; H,6.71; N,4.44;O, 5.07. Found; C, 83.82:H, 6.75;N,4.46;O,5.10

(2c) 2, 3, 4, 9-tetrahydro-1H-carbazol-1-yl-3-(4-methoxyphenyl) prop-2-en-1-one

IR (KBr) :3448,1668,2986 cm^{-1};^{1}H NMR: δ1.48-1.65(m,2H), 1.86(q, 2H), 2.74 (t,2H), 3.14 (m, 1H), 3.74(s,3H), 7.10-7.22 (m, 4H),7.26–7.45 (m, 4H), 7.45-7.47 (d, 2H, J = 9 Hz, vinylic hydrogen), 7.86(b s, 1H, NH). ^{13}CNMR: δ 21.6, 25.2, 50.3, 55.9 108.3, 111.1, 114.2, 119.0, 120.4, 126.3, 127.4, 127.3, 129.0, 131.0, 132.2, 136.2, 137.6,142.9 , 159.9, 197.6.MS(EI):m/z331.16 [M.$^+$]; yield :82%; mp: 68^{0}C;C_{22} $H_{21}NO_2$ Anal.Calcd.: C,79.73; H,6.39; N,4.23;O, 9.66. Found; C, 79.78;H, 6.37;N,4.26; O,9.70

(2d) 2, 3, 4,9-tetrahydro-1H-carbazol-1-yl-3-(2,4-dichlorophenyl)prop-2-en-1-one

IR(KBr) :3442,1666, cm^{-1};^{1}H NMR : δ 1.40 (m,2H), 1.88(q,2H), 2.71(t,2H), 3.15 (m,1H), 7.09-7.20 (m,3H),7.25-7,43 (m,4H), 7.45-7.47 (d,2H,J=9Hz, Vinylic hydrogen), 8.02(bs,1H, NH). ^{13}CNMR: δ 21.2, 25.4, 25.9, 50.1, 108.3, 110.1, 119.2, 120.1, 122.2, 126.3, 126.9, 127.4, 129.2, 131.1, 131.2, 132.6, 134.9, 136.2, 142.9, 197.6.MS(EI):m/z369.07 [M.$^+$]; yield :86 %;mp:113^{0}C ;C_{21} H_{17} Cl_2NO Anal. Calcd.: C,68.12; H,4.63;Cl,19.15;N,3.78;O, 4.32. Found; C, 68.14;H,4.65;Cl,19.17;N,3.82;O, 4.35

(2e)2,3,4,9-tetrahydro-1H-carbazol-1-yl-3-(2-methoxy,2-methyoxyphenyl) prop-2-en-1-one

IR (KBr) :3442,1666,2893,1370 cm^{-1} ;1H NMR: δ 1.25 (s,3H), 1.40 (m,2H,), 1.57 (s ,3H), 1.87(q, 2H), 2.78 (t,2H), 3.1 (m, 1H), 7.08-7.24 (m, 3H),7.25 -7.47 (m, 4H), 7.47-7.49 (d, 2H, J = 9 Hz, vinylic hydrogen), 7.90 (b s, 1H, NH). ^{13}CNMR: δ20.3, 21.2, 25.4, 50.2, 56.3, 107.6,108.3, 111.8, 113.8,119.0, 120.2, 122.3, 126.3, 127.4, 127.8, 129.2, 131.2, 136.2, 142.9, 151.6, 158.1, 169.0, 197.6. MS(EI): m/z389.15 [M.$^+$]; yield : 81%;mp:105^{0}C ;C_{24} $H_{23}NO_4$ Anal. Calcd.: C,74.02;H,5.95; N,3.60;O, 6.43. Found; C, 74;07,H, 5.92;N,3.66;O,6.47

(2f) 2,3,4,9-tetrahydro-1H-carbazol-1-yl-3-(2-nitrophenyl)prop-2-en-1-one

IR (KBr) :3442,1666, cm^{-1} ;^{1}HNMR : δ1.40-1.42 (m,2H), 1.87(q,2H), 2.71 (t,2H), 3.17 (m,1H), 7.05-7.32 (m,4H),7.47–7.49 (m,4H), 7.47-7.49 (d,2H, J = 9 Hz, Vinylic hydrogen), 7.92(bs,1H, NH). ^{13}CNMR: δ 21.2, 25.2, 25.9, 50.1, 108.1, 111.1, 119.0, 120.1, 121.0, 122.2, 126.3, 127.3, 127.4, 128.9, 130.0, 131.1, 134.8, 136.2, 142.9, 146.1, 197.6MS(EI):m/z346.13 [M.$^+$]; yield :89 %;mp:105^{0}C;C_{21} H_{18} N_2O_3 Anal. Calcd.: C,72.82; H,5.24; N,8.09; O, 13.86. Found; C, 72.86H, 5.28;N, 8.12;O, 13.89.

(2g) 2,3,4,9-tetrahydro-1H-carbazol-1-yl-3-(furan-2-yl)prop-2-en-1-one

3.b1H NMR : IR (KBr) :3446,1676,1835 cm^{-1} ; ^{1}HNMR:δ 1.43 -1.46 (m,2H,), 1.98(q,2H), 2.78 (t,2H), 3.16 (m,1H), 7.10-7.17 (m,3H),7.26 -7.26 (m,4H), 7.46-7.49 (2H, d, J = 9 Hz, Vinylic hydrogen), 7.92(1H, bs, NH). ^{13}CNMR: δ21.3, 25.3, 26.0, 49.5, 108.3, 111.4, 19.4, 112.7, 119.0, 120.1, 122.3, 127.4, 130.0, 131.2, 132.3, 136.3, 146.1, 151.6, 197.6.MS(EI):m/z291.13 [M.$^+$]; yield :85 %;mp:88^{0}C ;C_{19} $H_{17}NO_2$;Anal. Calcd.: C,78.33;H,5.88;N,4.81;O, 10.98. Found; C, 78.36; H,5.90;N,4.84;O, 10.94

General procedure for the preparation of isoxazolyl 2,3,4,9-tetrahydro-1H-carbazoles 3a-g

A mixture of 2,3,4,9-tetrahydrocarbazolyl chalcones **(2a-g)** (3mmol) in ethanol and anhydrous sodium acetate (3mmol)dissolved in minimum amount of acetic acid was added to a solution of hydroxylamine hydrochloride (3mmol)in ethanol (30ml). The reaction mixture was refluxed on a water bath for 8hour, concentrated and neutralized with sodium hydroxide. The product was isolated and recrystallized from ethanol to

give **(3a-g)**

(3a) 2,3,4,9-tetrahydro-1-(4,5-dihydro-5-phenylisoxazol-3-yl)-1H-carbazole

IR KBr ;3445, 1778 cm^{-1}; ^{1}H NMR : δ 1.32-1.34 (m, 2H),1.9 (q,2H), 2.2-2.25(d,2H,isoxazoleCH_2), 2.52 (t,2H), 2.8 (t,1H), 2.9(s,1H,isoxazoleCH),7.2-7.6 (m,4H), 6.5-7.12(m,5H),7.75 (bs,1H, NH) ^{13}CNMR: δ 22.5, 25.2, 25.4, 37.6,47.0, 81.3, 108.3, 111.1, 119.0, 120.1, 122.2, 127.2, 127.4, 127.7, 129.0, 131.1, 136.2, 140.7, 164.6.MS(EI): m/z 316.16. [M^{+1}];yield: 65%; mp:102^{0}C; $C_{21}H_{20}N_2O$ Anal.Calcd.; C,79.72; H,6.37.; N,8.85.; O, 5.0 Found; C, 79.74;H, 6.39.;N, 8.88.;O,5.10

(3b) 2,3,4,9-tetrahydro-1-(4,5-dihydro-5-p-tolyl-isoxazol-3-yl)-1H-carbazole

IR KBr ;3448,1782 cm^{-1};^{1}H NMR : δ 1.20 - 1.28(m,2H) 1.6(s,3H),1.8 (q,2H),2.1-2.15(d,2H, isoxazoleCH_2), 2.52(t,2H),2.8(t,1H), 2.9 (s,1H, isoxazoleCH), 7.3-7.6(m,4H), 6.52-7.13(m,4H)7.74 (bs,1H, NH) ^{13}CNMR: δ22.5, 25.2, 25.4, 37.6, 47.0, 81.3, 108.3, 111.1, 119.0, 120.1, 122.2, 127.2, 127.4, 127.7, 129.0, 131.1, 136.2, 137.7, 140.7 , 164.6. MS (EI): m/z330.17. [M^{+1}]; yield :69 %;mp: 89^{0}C;$C_{22}H_{22}N_2O$Anal. Calcd.: C,79.97; H,6.71. ; N,8.48.; O,4.84. Found; C, 79.94; H, 6.69; N, 8.46.; O, 4.83.

(3c) 2,3,4,9-tetrahydro-1-(4,5-dihydro-5-(4-methoxyphenyl)-isoxazol-3-yl)-1H-carbazole

IR KBr;3443,1786 cm^{-1};^{1}H NMR : δ1.60-1.68 (m,2H),1.7(s,3H), 1.9 (q,2H),2.20-2.23 (d,2H, isoxazole CH_2), 2.54 (t,2H), 2.8(t,1H), 2.91 (s,1H, isoxazole CH), 7.4-7.6(m,4H), 6.70-7.73(m,4H),7.76 (bs,1H, NH) ^{13}CNMR: δ22.5, 25.2, 25.4, 37.6, 47.0, 55.9, 81.3,108.3, 111.1,119.0, 120.1, 127.2, 127.4, 127.7, 129.0, 131.1, 136.2, 137.7,140.7, 159.6, 164.6.MS(EI):m/z346.17. [M^{+1}]; yield: 89 %; mp:128^{0}C ;$C_{22}H_{22}N_2O_2$ Anal. Calcd: C, 76.28; H, 6.40.;N,8.09;O,9.24. Found; C,76.32; H,6.46; N,8.12; O,9.22

(3d) 2,3,4,9-tetrahydro-1-(4,5-dihydro-5-(2,4 dichlorophenyl) -isoxazol-3-yl)-1H-carbazole

IR KBr ;3446,1784,880cm^{-1};^{1}H NMR: δ1.50-1.62(m,2H),1.90 (q,2H),2.22-2.24 (d,2H,isoxazole CH2),2.53(t,2H),2.82(t,1H,) 2.90(s, 1H, isoxazole CH), 7.3-7.5(m,4H), 6.7-7.20(m,3H),7.77 (bs,1H, NH) ^{13}CNMR: δ 23.5, 26.2,25.3, 35.6,46.0, 54.9, 82.3, 108.2,112.5, 119.6, 121.1,127.2, 124.4, 126.7, 129.4, 132.1, 135.2, 138.7, 133.9, 142.7, 159.4, 163.6.MS(EI):m/z384.08. [M^{+1}]; yield :88 %;mp: 102^{0}C ;$C_{21}H_{18}Cl_2N_2O$ Anal. Calcd.: C,65.46; H,4.71; Cl,18.40; N,7.27;O,4.15. Found; C, 65.46; H, 4.74.; Cl, 18.44;N, 7.29; O,4.13.

(3e) 2,3,4,9-tetrahydro-1-(4,5-dihydro-5-(2-methoxy,4methyoxyphenyl)-isoxazol-3-yl)-1H-carbazole

IR KBr ;3445,1783,1671,2993cm^{-1}; ^{1}H NMR : δ 1.45-165 (m,2H), 1.7(s,3H), 1.78(s,3H), 1.9(q,2H), 2.21-2.24 (d,2H,isoxazoleCH_2), 2.52(t,2H), 2.81 (t,1H,CH), 2.90 (s,1H,isoxzoleCH), 7.4-7.62 (m,4H), 6.78-7.30 (m,3H), 7.75(bs,1H,NH) ^{13}CNMR :δ23.7, 26.4, 25.8, 35.2, 46.0, 46.6, 54.7, 82.8, 108.4, 112.7, 118.6,124.1, 124.2, 127.7,128.1, 130.4, 131.1, 133.9, 134.2, 135.1, 142.7, 159.4, 163.6 ; MS(EI) : m/z404.79 [M^{+1}]; yield : 86%;mp:76^{0}C ;$C_{24}H_{23}NO_4$ Anal. Calcd.: C,71.27;H,5.98;N,6.93;O, 15.82. Found; C,71;32,H,5.94;N,6.96;O,15.79.

(3f) 2,3,4,9-tetrahydro-1-(4,5-dihydro-5-(2-nitrophenyl)-isoxazol-3-yl)-1H-carbazole

IR KBr ;3445, 1783, 1671,cm^{-1} ;^{1}HNMR : δ1.45-165(m,2H),1.92 (q,2H),2.20-2.24 (d,2H,isoxazole CH_2), 2.54(t,2H), 2.84(t,1H), 2.92(s,1H,isoxzoleCH), 7.41-7.60(m,4H) 6.72-7.32 (m,3H),7.87 (bs,1H, NH) ^{13}CNMR: δ23.8, 26.4, 25.8, 35.2, 46.0, 46.6, 54.7, 82.8,108.4,112.7,118.6,130.4,131.1,133.9, 134.2, 135.1, 136.0 ,138.7;MS(EI):m/z361.14. [M^{+1}]; yield: 92%; mp:121^{0}C ;$C_{21}H_{19}N_3O_3$ Anal. Calcd.: C,69.79; H,5.30; N,11.63; O, 13.28. Found; C, 69.82; H, 5.34;N,11.68;O, 13.24.

(3g) 2,3,4,9-tetrahydro-1-(4,5-dihydro-5-(furan-2-yl)-isoxazol-3-yl)-1H-carbazole

IR KBr ;3445, 1784, 1672,cm^{-1} ; ^{1}H NMR : δ1.56 -1.62(m,2H),1.90 (q,2H),2.20-2.23(d,2H, isoxazole CH2), 2.53(t,2H,), 2.80 (t,1H) 2.94 (s,1H,isoxzoleCH), 7.40-7.60(m,4H), 6.72-7.32 (m,3H,)7.82 (bs,1H, NH) ^{13}CNMR:δ23.7, 26.4,25.8,35.2,45.2,46.0,46.6,54.7, 118.6,124.1,124.2,127.7, 128.1,130.4,131.1, 133.9, 134.2,MS(EI):m/z 306. 14[M^{+1}]; yield: 85%; mp:96^{0}C; $C_{19}H_{18}N_2O_2$ Anal.Calcd. :C,74. 49; H,5.92; N,9.14;

O,10.44. Found; C,74.44; H,5.95;N,9.11;O,10.48

General procedure for the preparation of pyrazolyl 2,3,4,9 tetrahydro-1H-carbazole (4a-g)

A mixture of 2,3,4,9 tetrahydrocarbazolyl chalcones **(2a-g)**(3mmol) and hydrazine hydrate (1.5mmol) in ethanol was refluxed . After a period of 2 hours the solvent was removed under reduced pressure and the residue was washed with water and extracted with chloroform and the combined organic layer were dried over the anhydrous sodium sulphate. Evaporation of the solvent followed by crystallization with petroleum ether-ethyl acetate yielded the desired compounds **(4a-g)**

(4a) -2,3,4,9-tetrahydro-1-(4,5-dihydro-5-phenyl-1H-pyrazol-3-yl)-1H-carbazoles

IR KBr ;3448, 1820, 1560 cm^{-1}; ^{1}H NMR : δ1.68-1.72(m,2H), 2.06-2.12 (m,2H), 2.73 (d,2H,Pryazole CH_2), 2.97(t,2H) ,3.15(t,1H) 6.44-6.74(m,4H),6.82-7.26(m,5H), 3.9 (t,1H), 7.63(s,1H,PyrazoleNH), 7.67(bs,1H,NH); ^{13}CNMR: δ21.8,25.2,26.2, 33.5, 37.9, 49.8,111.1,119.0,120,122.2,126.8,127.0, 127.4, 128.6, 136.2. MS (EI): m/z315.17 [M^{+1}]; yield: 50%;mp:92^{0}C; $C_{21}H_{21}N_3$ Anal.Calcd.: C,79.97; H,6.17; N,13.32; Found; C,79.94;H,6.1 N,13.38;

(4b) 2,3,4,9-tetrahydro-1-(4,5-dihydro-5-tolyl-1H-pyrazol-3-yl)1H-carbazole

IR KBr ;3446, 1828, 1564cm^{-1};^{1}H NMR : δ1.66-1.76 (m,2H), 1.8(s,3H),2.05-2.16 (m,2H), 2.76 (d,2H, Pryazole CH_2), 2.87(t,2H), 3.12(t,1H),6.47-6.74 (m,4H),6.8-7.25(m,4H),3.8(t, 1H),7.67 (s,1H, PyrazoleNH),7.77 (bs,1H, NH); ^{13}CNMR: δ21.8, 24.3, 25.2, 26.2, 26.9, 33.5, 37.9 ,40.5, 49.8, 111.1, 119.0, 120.1, 122.2, 126.8, 126.9, 127.0, 127.4, 128.6, 128.9, 136.2, 136.4.MS(EI): m/z329.19 [M^+]; yield :92 ;mp:130^{0}C ;$C_{22}H_{23}N_3$ Anal. Calcd.: C,80.21; H,7.04;N,12.76; Found; C,80.25;H,7.08;N,12.80;

(4c) 2,3,4,9-tetrahydro-1-(4,5-dihydro-5-(4methoxy phenyl)-1H-pyrazol-3-yl)-1H-carbazole

IR KBr ;3452,1827,1560 cm^{-1}; ^{1}H NMR : δ1.67-1.77 (m, 2H), 1.89 (s,3H) ,2.07-2.18 (m,2H), 2.74(d,2H , PryazoleCH$_2$),2.96 (t,2H), 3.18(t,1H) 6.44-6.45 (m ,4H),6.69-6.82(m,4H),3.44 (t,1H), 7.54-7.52 (t,1H), 7.63(s, 1H,PyrazoleNH) 7.67 (bs,1H, NH) ^{13}CNMR: δ 21.8, 25.2, 26.2, 33.5, 37.9, 49.8, 55.9, 111.1, 114.1, 119.0, 120.1, 122.2,126.8,127.0,127.4,128.6, 136.2,158.7MS(EI):m/z345.18 [M^+]; yield :82% ; mp:110^{0}C; $C_{22}H_{23}N_3O$ Anal.Calcd.:C,76.49; H,6.71; N,12.16;O,4.63.Found;C,76.52;H,6.7 6 ; N,12.11; O,4.68;)

(4d) 2,3,4,9-tetrahydro-1-(4,5-dihydro-5-(2,4 dichlorophenyl)-1H-pyrazol-3-yl)-1H-carbazole

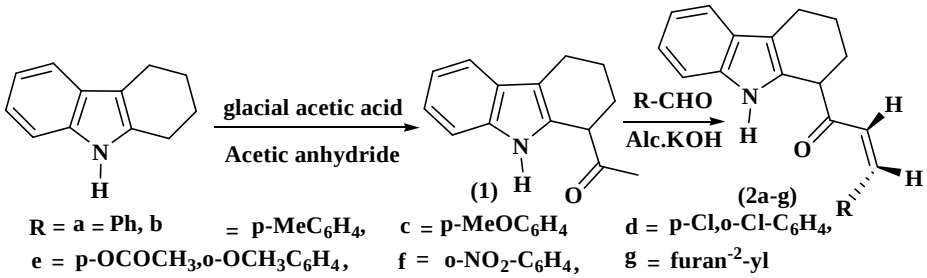
IR KBr ;3447,1826,1568 cm^{-1}; ^{1}H NMR : δ1.68-1.78 (m,2H), 2.06-2.12 (m,2H), 2.73(d,2H, PryazoleCH$_2$), 2.97 (t,2H), 3.15(t,1H) 6.44-6.74(m,4H),6.82-7.26 (m,3H), 3.9(t,1H), 7.63 (s,1H,PyrazoleNH),7.67 (bs, 1H, NH); ^{13}CNMR: δ 23.8, 27.2, 27.2, 34.5, 38.9, 45.8, 110.1, 116.0, 122., 122.2,125.8, 127.0, 127.4, 128.6, 136. MS(EI):m/z383.10 [M^+]; yield :95%; mp:134^{0}C ;$C_{21}H_{19}ClN_3$ Anal. Calcd.: C,65.63;H,4.98; Cl,18.45; N,10.93.Found; C,65.67;H,4.92; Cl,18.49; N,10.98.;

(4e)2,3,4,9-tetrahydro-1-(4,5-dihydro-5-(2-methoxy,4methyoxyphenyl)-1H-pyrazol-3-yl)-1H-carbazole

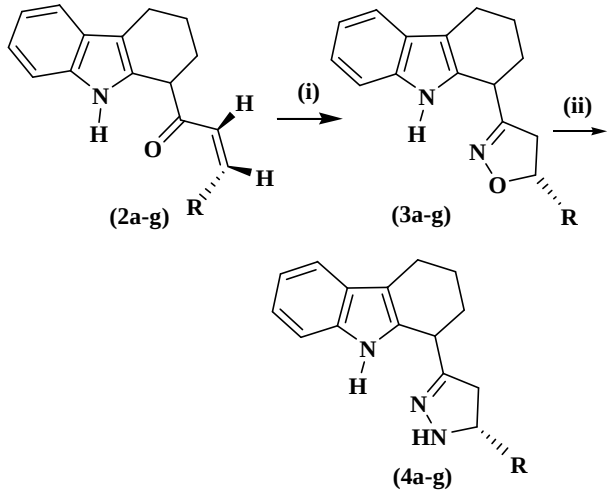
IR KBr; 3447,1826,1568 cm^{-1}; ^{1}H NMR : δ 1.25(s,3H) 1.68-1.72(m,2H),1.89(s,3H), 2.06-2.22 (m,2H), 2.74(d,2H PryazoleCH$_2$),2.99 (t,2H, t), 3.16(t,1H),6.69-6.74(m,4H),7.0-7.26 (m,3H), 3.46(t1H), 7.54-7.52(t,1H),7.63(s,1HPyrazo-le NH),7.76 (bs,1H ,NH) ^{13}CNMR: δ20.3, 21.8, 25.2, 26.2, 33.5, 37.9, 49.8, 55.9, 107.5,111.1,114.1, 119.0,120.1, 127.4,128.6,136.2,158.7,169.0. MS (EI): m/z403.20 [M^+]; yield :83%;mp:108^{0}C; $C_{24}H_{25}N_3O_3$ Anal. Calcd.: C,71.44; H,6.25;N,10.41; O, 11.90. Found; C,71; 47, H,6.22; N,10.46; O,11.94

(4f) 2,3,4,9-tetrahydro-1(4,5-dihydro-5-(2-nitro phenyl)-1H-pyrazol-3-yl)-1H-carbazole

IR KBr ;3448,1825,1556 cm^{-1}; ^{1}H NMR : δ1.67-1.72(m,2H), 2.05 -2.14(m,2H), 2.74 (d,2H,Pryazole CH$_2$), 2.96(t,2H),3.12(t,1H),6.82-7.26(m,4H),3.8 (t,1H), 7.32-7.42(m,4H),7.66(s,1H,PyrazoleNH),7.66 (bs,1H, NH); ^{13}CNMR: δ21.8, 25.2, 26.2, 33.5, 37.9,49.8,111.1,119.0,120.,122.2,126.8,127.0, 127.4, 128.6, 136.2. MS(EI): m/z315.17 [M^{+1}]; yield : 50%;mp:92^{0}C ;$C_{21}H_{21}N_3$ Anal. Calcd.: C,79.97; H,6.17;N,13.32; Found; C,79.94; H,6.13; N,13.38; MS(EI):m/z360.16[M^+]; yield :88% ;mp:113; $C_{21}H_{20}N_4O_2$ Anal. Calcd.: C,69.98;H,5.59; N,15.55;



SCHEME 1: Synthesis of chalconyl carbazoles



SCHEME 2 : Reagents and coditions: (i) Anhydrous CH_3COONa, CH_3COOH, $NH_2OH.HCl$, 50^{0}C, 8h; (ii) NH_2NH_2.80%H_2O/ethanol

O,8.88.Found; C,69.92;H,5.62; N,15.60;O,8.80;

2,3,4,9-tetrahydro-1-(4,5-dihydro-5-(furan-2-yl)-1H-pyrazol-3-yl)-1H-carbazole (4g)

IR KBr ; 3454,1830,1557 cm^{-1}; ^{1}H NMR : δ1.69-1.72(m,2H), 2.15-2.14 (m,2H), 2.64 (d,2H,Pryazole CH_2), 3.108 (t,2H), 3.12(t,1H),6.82-7.26(m,7H),3.6 (t,1H), 7.62 (s,1H,PyrazoleNH),7.68 (bs,1H, NH); ^{13}CNMR: δ21.6, 25.4, 26.3, 35.5, 38.9, 49.7, 101.1,118.0,120., 121.2,126.8, 127.0, 128.4, 129.6, 136.2.MS(EI):m/z315.17 [M.$^+$]; yield :85%;mp:92^{0}C ;$C_{21}H_{21}N_3$ Anal. Calcd.: C,79.97;H,6.17;N,13.32; Found; C,79.94; H,6.13; N,13.38; O,5.25

RESULTS AND DISCUSSION

Acetylation of 2,3,4,9 tetrahyro-1H-carbazole using acetyl chloride in glacial acetic acid afforded 1-acetyl tetrahydrocarbazole(1) and moderate yield is reported[17] (SCHEME 1). The ^{1}HNMR spectrum of (1) showed a broad signal for N-H at δ 7.8 ppm as that in tetrahy drocarbazole. Its IR spectrum also showed two bands at 3410 and 3275cm^{-1} for two N-H stretching vibrations. The multiplets at δ3.15 showed the presence of deshielded methine at the 1st position of tetrahy drocarbazole. From the aforesaid facts it was clear that the acetylation taking place at 1st position of tetrahydrocarbazole and further the acetylation not reacted at with imine hydrogen of tetahydocarbazole.

When 1-acetyl tetrahydrocarbazole**(1)** was treated with substituted aryl aldehydes in presence of alcoholic potassium hydroxide as catalyst afforded, 2,3,4,9 tetrahydrocarbazolyl-chalcones **(2a-g)**. ^{1}HMR signals for the aryl hydrogens of chalcons appeared at 7.0 - 7.12 as multiplet. In the ^{1}HMR spectra of the compounds **(2a-g)**, each one consistently showed a signal at 7.45 - 7.47 (2H, d, J = 9 Hz, syn) for the presence of vinylic protons of 2,3,4,9tetrahydrocarbazolyl-chalcones. It is inferred that the phenyl group attached in the carbazolyl chalcones may be in opposite plane to that of the vinylic hydrogens.

The compounds **(2-4,9)** tetrahydrocarbazolyl-chalcones **(2a-g)** underwent cyclization with hydrazine hydrate, afforded excellent yields of 2,3,4,9-tetrahydro-1-pyrazolyl- 1H-carbazole **(4a-g)** (SCHEME 2). In the ^{1}HNMR spectrum of **(4e)**, the signals for methyl protons of acetyloxy and methoxy appeared at 1.25 and 1.89 ppm respectively. The pyrazolyl methylene protons and chiral methine proton appeared at 2.73-2.76 ppm and 2.97 ppm respectively along with 2,3,4,9 tetrahydrocarbazole protons. Abroad peak for N-H appeared at 7.63 ppm.

Another class of 2,3,4,9-tetrahydro-1-isoxazol-3-yl)-1H-carbazole **(3a-g)**have been synthesized by refluxing hydroxylamine hydrate with 2,3,4,9 tetrahydro carbazolyl-chalcones **(2a-g)** (SCHEME 2). In the ^{1}HMR spectrum of 2,3,4,9-tetrahydro-4,5-dihydro-5-(2-methoxy,4methyoxyphenyl)-isoxazol-3-yl)-1H-car-

bazole **(3e)**, isoxazolyl methylene protons and methine proton appeared at 2.2 - 2.5ppm and 2.52ppm respectively along with 2,3,4,9 tetrahydrocabazole protons. The signal for methyl proton of acetyloxy and methoxy respectively showed at 1.5 and 1.7 ppm. A broad peak for N-H appeared at 7.75ppm. Aromatic protons appeared as multiplets at 6.5 ppm and 7.2-7.6 ppm. A quartet at 1.9 ppm ,triplet at 2.8 ppm and 2.52 ppm and multiplet at 1.3 ppm appeared for the cyclohexyl protons.

Antibacterial activities of all the newly prepared compounds against nine bacteria are presented in TABLE 1. The antibacterial activity of compounds **(3d)** and **(4d)** and **(3c)** and **(4a)** are respectively having methoxy groups and chloro groups in heteocyclic moieties is quite good. The compounds 3e and 4e having acetyloxy and methoxy groups exhibited more pronounced activities than other compounds . The compounds **(3a)** and **(4a)** exhibit moderate activity against all the tested bacteria. (Shown in TABLE 1)

Antifungal activities of all the newly prepared compounds against nine bacteria are presented in TABLE 1. The antibacterial activity of compound **(3c)** and **(3d)** are respectively having excellent activity towards Fusarium oxysporum and Altenaria macrospore among tested the four organism. Compounds **(3b)** and **(4b)** are exhibit the moderate activity whereas **(3g)** and **(4g)** exhibited poor activity for the tested organisms (Shown in TABLE 2).

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