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# Synthesis of Tetrahydro Carbazoles And Tetrahydro-Γ-Carbolines Catalyzed By PEG-400 As Recyclable Reaction Medium

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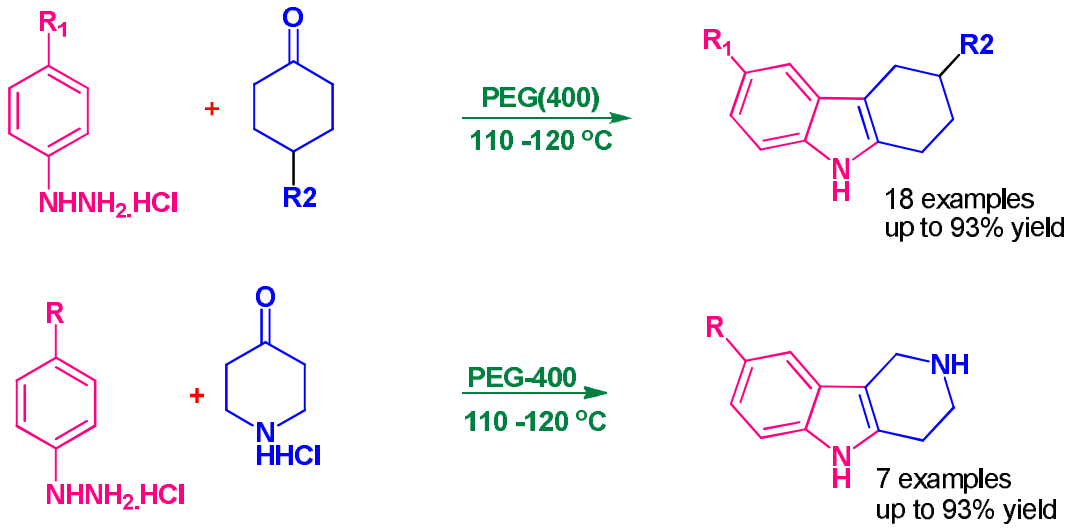
## ABSTRACT

*Simple and efficient synthesis of substituted tetrahydrocarbazoles and tetrahydro-γ-carbolines from the ketones and substituted hydrazine hydrochlorides in polyethylene glycol (PEG-400).*

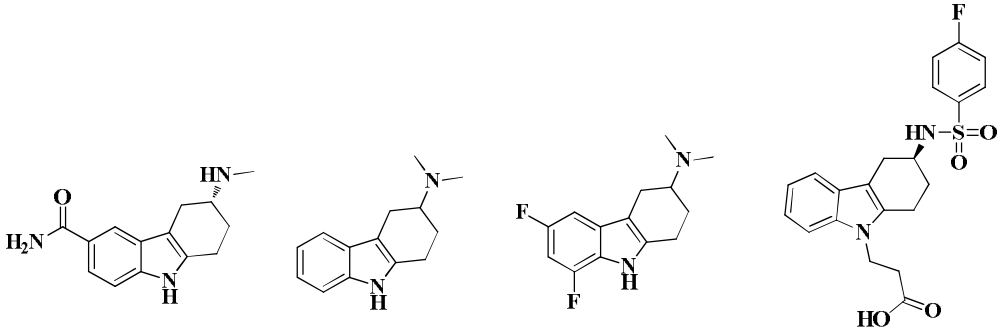



**Keywords:** Cyclisation, Phenylhydrazinehydrochloride, Cyclohexanone, 4-Piperidone, Tetrahydrocarbazole, Tetrahydro-γ-carbolines, PEG-400.

## INTRODUCTION

Thrust in the preparation of carbazole skeletons is increasing due to the significant biological profiles exhibited by the molecules having these skeletons isolated from natural sources and their synthetic derivatives prepared in the laboratory. The paramount importance of heterocycles such as indoles[1] and their derivatives in natural product chemistry and pharmacology constantly drives the search for the new procedures for their construction and also for the preparation of variety of their derivatives to exploit their biological activity.

Substituted 2,3,4,9-tetrahydro carbazoles and tetrahydro-γ-carbolines are the class of indole alkaloids that have been reported to possess an array of biological properties including central nervous system activity, antihistamine[2], antidiabetic, antipsychotic (or neuroleptic)[3] and anti-inflammatory properties[4]. Also, they are important as intermediates for the production of pharmaceutically active compounds like Frovatriptan (1), Flucindole (2), Ramatroban (3) and Ciclindole (4) **(Fig .1)**




**Frovatriptan** **Ciclindole** **Flucindole** **Ramatroban**

**Fig .1** Substituted tetrahydrocarbazole derivatives.

Further they are also been used as building blocks for potential electroluminescent materials, polymers with useful electrical and thermal properties.

Over the past decades a large number of biologically active carbazole alkaloids have been obtained from terrestrial plants, marine resources and streptomycetes [5]. Development of new methods for the synthesis of functionalized carbazoles in particular, is attracting organic chemists due to the discovery of many carbazole alkaloids with varied pharmacological properties[6]. The emerging importance towards the various strategies applied to prepare carbazoles was due to their diverse pharmacological derivatives [7]. Recent discovery explore the cascade reaction sequences for the synthesis of biologically active organic compounds having substituted 2,3,4,9-tetrahydro carbazoles[8] frame work.

A number of reports have been showed that tetrahydro-γ-carbolines or pyrido(4,3-*b)* indoles have various biological activities in antipsychotic[9], antibiotic[10], and antitumor[11] fields, although studies of their chemical activities are limited compared to those of tetrahydro-γ-carbolines or pyrido(3,4-*b)*indoles, structurally related to tryptophan and serotonin. □-Carbolines can be synthesized using various methods like the Graebe- Ullmann procedure[12], Pictet-Spengler cyclization, Fischer annulation [13], ring closure of aldimine [14], Suzuki-type reaction [15], intramolecular Diels-Alder reaction [16] or Pd-catalyzed annulation of alkynes, Jean-Pierre Hénichart [17] reported in acidic conditions.

Organic reactions in Poly Ethylene Glycol have attracted the attention of researchers because of the added advantages of PEG has an ability to act as phase transfer catalyst and its eco-friendly nature when compared to other "neoteric solvents" such as ionic liquids, super-critical fluids and micellar systems[18]. PEG is a polymerized ethylene oxide having hydrophilic nature and it has some benign characteristic properties with respect to environment and chemical industry such as less-toxic, less-expensive, easy to handle, thermally stable, reduced flammability and more over it can be easily recyclable in different organic reaction transformations such as substitution reactions[19], oxidation and reduction reactions[20] ,Heck reaction[21], asymmetric dehydroxylation[22], Whacker reactions[23], in partial reduction of alkynes[24], Suzuki cross coupling reaction[25], among them synthesis of β-amino sulfides, β-keto

sulfones, dibenz[b,f]-1,4 oxazepines[26]. Benzimidazoles and bis-benzimidazoles, 3,4-dihydropyrimidinones and several more were reported using PEG as recyclable medium[27].
In general, synthesis of carbazole frame work is carried out by multistep fisher reaction[28] which requires the usage of organic solvents with very meager product yields. Hence a simple and efficient method for the synthesis of these pharmaceutically important classes of compounds is highly desirable precluding the usage of organic solvents.
Substituted phenyl hydrazine's were treated with varying amounts of cyclohexanone under different conditions by choosing different reagents and acids to yield 1,2,3,4-tetrahydrocarbazoles. In presence of acetic acid, zinc chloride and hydrochloric acid lesser amount of the desired products were obtained. The reactions proceeded slowly, and the yields were very low with a lot of uncyclized intermediates in acidic conditions and also quenching of the reagents is very critical. The effect of solvents was also investigated. In alcoholic solvents yields are low because of reactions are stopped at hydrazone stage. Finally we observed better yield in PEG-400 without using any reagent and catalyst. Yields are poor at lower temperatures. Ideal temperature for the reaction was observed at 110-120°C. Similarly tetrahydro-γ-carbolines were prepared by reaction of substituted phenyl hydrazine's with 4-piperdone hydrochloride.

## MATERIALS AND METHODS

All the reagents and starting materials used in this study are of reagent grade which were procured from Sigma Aldrich and were used as received. All melting points were uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 1650 spectrophotometer (USA). $^1$H- NMR spectra were determined on a Varian (400 MHz) spectrometer and chemical shifts were expressed as Ms-QP 1000EX, Shimadzu, Japan). All compounds prepared in this paper are confirmed with spectral data

**General Procedure for substituted tetrahydro carbazoles synthesis:** To a stirred solution of Polyethylene glycol (PEG-400) (5 mL), substituted phenyl hydrazine (1.0 mmol), Cyclohexanone (1.0 mmol) were added, after which the reaction mixture was heated at 110-120$^o$C until completion of the reaction as indicated by TLC. After completion of stating material (as monitored by TLC). Reaction mixture was diluted with ice cold water and stirred at 0 $^o$C for 15 min solids was formed it was collected by filtration (Table 1). The product was confirmed by IR, 1H & 13C NMR, mass spectra and compared with authentic samples known in literature.

**General Procedure for substituted tetrahydro γ-carboline synthesis:** To a stirred solution of Polyethylene glycol (PEG-400) (5 mL), substituted Phenyl hydrazine (1.0 mmol), piperidin-4-one (1.0 mmol) were added, after which the reaction mixture was heated at 110-120 $^o$C until completion of the reaction as indicated by TLC. After completion of stating material (as monitored by TLC). Reaction mixture was diluted with ice cold water and stirred at 0 $^o$C for 15 min solids was formed it was collected by filtration (Table 2d). The product was confirmed by IR, $^1$H & $^{13}$C NMR, mass spectra and compared with authentic samples known in literature.

**1,2,3,4-tetrahydrocarbazole (Table-1,entry 1) :**Pale brown solid, m.p. 114-116 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 1.91-1.96 (br m, 4H), 2.74-2.78 (m,4H), 7.08-7.17 (m, 2 H), 7.3 (d, 1 H), 7.49 (d, 1 H), 7.68 (br s, 1 H) ; $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 20.05, 22.20, 22.32, 22.42, 108.98, 109.61, 116.81, 118.12, 119.96, 126.82,133.30,134.66 IR(neat)cm$^{-1}$:3401, 2928, 2848, 1470,1305,1235, 739 ; Anal.Calcd for $C_{12}H_{13}N$:C,84.17; H,7.65; N, 8.18. Found:C,82.87;H,7.53; N, 7.84.

**6-Methyl-2,3,4,9-tetrahydro-1H-carbazol (Table-1,entry 2):** Off white solid, m.p. 140-142 $^o$C; $^1$H NMR ($CDCl_3$): d 7.57 (br, NH), 7.24 (s, 1H), 7.16 (d, J ¼ 8.0 Hz, 1H), 6.93 (d, J ¼ 8.0 Hz, 1H), 2.72–2.66 (m, 4H), 2.17 (s, 3H), 1.92–1.84 (m, 4H); (IR (KBr): n 3393 (NH), 3022 (ArH), 2925, 2846, 1589, 796 cm21;anal. calcd. for C13H15N: C, 84.28; H, 8.16; N, 7.56. Found C, 84.12; H, 8.37; N, 7.19

**6-Methoxy-2,3,4,9-tetrahydro-1H-carbazol ( Table-1,entry 3):** Pale yellow solid. m.p. 106-108 $^{o}$C; $^{1}$H NMR ($CDCl_3$, 400 MHz) : $\delta$ ppm 7.56 (br s, 1 H), 7.15 (d, 1 H), 6.95 (d,1 H), 6.88 (dd, 2.4 Hz, 1H), 3.87 (s, 3 H), 2.73–2.69 (m, 4 H), 2.67–1.89 (m, 4 H).;$^{13}$CNMR(DMSO-$D_6$ 400$MH_z$):155, 135.3, 132, 128.1, 112.5, 112.2, 106, 105.5,55.9,35.5,35.2,26.5,25.0;IR (KBr)cm$^{-1}$:3381,3387,1620,1448,1367, 1055,742. Anal. calcd. for C13H15NO:C,77.58; H,7.51;N,6.96.Found C,77.94; H,7.82; N, 6.82.

**6-Fluoro-2,3,4,9-tetrahydro-1H-carbazol (Table-1,entry 4):** Off white solid, m.p. 107-109$^{o}$C ;$^{1}$H NMR ($CDCl_3$, 400 MHz) : $\delta$ ppm 7.65 (br, NH), 7.17 (m, 1H), 7.10 (dd, 1H), 6.86–6.81 (m, 1H), 2.73–2.64 (m, 4H), 1.94–1.84 (m, 4H); $^{13}$C NMR (DMSO-$D_6$ 400$MH_z$) : 154, 134.3, 132, 130.7, 112.5, 112.4, 107, 106.5, 35.5, 35, 26.5, 24.5. IR (KBr) cm$^{-1}$ : 3395,3386, 1620, 1448, 1367, 1055, 742; MS (ESI) : *m/z* 190[M+H]$^{+}$ anal.calcd. for C12H12FN: C, 76.17; H, 6.39; N, 7.40. Found C, 76.54; H, 6.02; N, 7.76.

**6-Chloro-2,3,4,9-tetrahydro-1H-carbazol ( Table-1,entry 5):** Brown colour solid; m.p. 140–141 $^{o}$C;1H NMR (CDCl3): d 7.71 (br, NH), 7.43 (d, J ¼ 2.0 Hz, 1H), 7.19 (d, J ¼ 8.0 Hz, 1H), 7.07 (dd, J ¼ 8.0, 2.0 Hz, 1H), 2.75–2.66 (m, 4H),1.96–1.85 (m, 4H); IR (KBr): n 3404 (NH), 2937, 2846, 1580, 1467, 800 cm$^{-1}$ anal. calcd. for C12H12ClN: C, 70.07; H, 5.88; N, 6.81. Found C, 69.80; H, 5.99; N, 6.68.

**6-Bromo-2,3,4,9-tetrahydro-1H-carbazol (Table-1,entry 6):** Pale yellow colour solid; m.p. 153-155 $^{o}$C;$^{1}$H NMR (CDCl3,400MHz): 7.63 (br s, 1 H), 7.58 (d, 1 H), 7.19 (dd,1.8 Hz, 1 H), 7.11 (d,1H), 2.73–2.64 (m, 4 H), 1.95–1.84 (m, 4 H).$^{13}$C NMR (75 MHz, CDCl3): d = 135.60, 134.26, 129.68, 123.59, 120.42, 112.32, 111.71, 110.01, 23.22, 23.14, 23.06, 20.76.; IR (KBr): 3400, 2938, 2906, 2848, 1578, 1434, 1310, 1232, 1046, 974, 862, 796 cm$^{-1}$.

**2,3,4,9-Tetrahydro-1H-carbazole-6-carbonitrile (Table-1,entry 7):** Brown colour solid; m.p. 123-125 $^{o}$C;$^{1}$H NMR (CDCl3,400MHz): 8.13 (br s, 1 H), 7.76 (s, 1 H), 7.19–7.49 (m, 2 H), 2.74 (t, *J* = 5.7 Hz, 2 H), 2.67 (t, *J* = 5.8 Hz, 2 H), 1.75–2.03 (m, 4 H); $^{13}$C NMR (75 MHz, CDCl3): 137.4, 136.6, 127.7, 124.1, 123.1, 121.2, 111.0, 111.0, 101.7, 23.1, 22.9, 22.8, 20.6.; IR (KBr): 3314, 2926, 2846, 2216, 1686, 1622, 1478, 1318, 1236, 1180, 872, 806, 798, 626 cm$^{-1}$

**2,3,4,9-Tetrahydro-1H-carbazol-3-ol (Table-1,entry 8) :** Off white solid; m.p. 132-133 $^{o}$C; $^{1}$H NMR ($CDCl_3$, 400 MHz): δ ppm 7.64 (br s, 1 H), 7.49(m,1H),7.29(m,1H), 7.08-7.71(m,2H),2.74(brt,4H),1.86-1.99(m,4H); $^{13}$CNMR($CDCl_3$, 400MH): δ 134.66, 133.3, 126.8, 119.9, 118.12, 116.8, 109.6, 108.3, 68, 33.7,31.3, 22.05; IR (KBr) cm$^{-1}$ : 3215, 2920, 1620, 1448, 1367, 1055, 742; Elemental Analysis: C, 76.98; H, 7.00; N, 7.48; O, 8.54 .MS (ESI) : *m/z* 188 [M+H]$^{+}$

**6-Fluoro-2,3,4,9-tetrahydro-1H-carbazol-3-ol (Table-1,entry 9):** Off white solid; m.p. 119-120$^{o}$C;$^{1}$HNMR($CDCl_3$,400MHz):$\delta$ppm7.6-7.9(brs,1H),7.0-7.2(m,2H), 6.8(t,1H, J=10Hz,J=4.8Hz),4.2-4.4(m,1H),3.0-3.05(m,1H,),2.86-2.95(m,3H),2.0-2.15(m,2H); $^{13}$C-NMR($CDCl_3$,400MHz): 158.8,156.5, 134.7, 132.7, 128.1, 110.9, 109.3, 107.4,102.9,67.3, 30.2, 20.4; IR (KBr) cm$^{-1}$: 3417 , 3250, 2920, 1585, 1483, 1450, 1354, 1170, 956, 800,744; MS (ESI) : *m/z* 204 [M-H]$^{+}$

**6-Chloro-2,3,4,9-tetrahydro-1H-carbazol-3-ol (Table-1,entry 10):** Brown color solid, m.p. 125-126$^{o}$C;$^{1}$HNMR($CDCl_3$,400MHz): $\delta$ ppm 7.9-8.0(brs,1H), 7.0-7.2 (s,1H),6.85-6.95(d,2H,J=8.2Hz), 4.2-4.4(m,1H), 3.0-3.05 (d,1H), 2.6-2.95(m,3H), 2.0-2.15(m,2H); $^{13}$CNMR($CDCl_3$,75MHz): 134.7,132.7,128.1,126.2,110.9,109.3,107.4,102.9,67.3,30.2,20.4.;IR(KBr)cm$^{-1}$3410,3230,2955,1585,1483, 1450,1354,1175;MS(ESI):*m/z*222 [M+H]$^{+}$

**6-Bromo-2,3,4,9-tetrahydro-1H-carbazol-3-ol (Table-1,entry 11):** m.p. 181-182$^{o}$C; $^{1}$HNMR ($CDCl_3$,400MHz): $\delta$7.6-7.9(brs,1H), 7.0-7.2(S,1H,), 6.85-6.9(d,2H,J=7.4Hz), 4.2-4.4 (m,1H), 3.0-3.05 (d,1H), 2.6-2.95 (m,3H), 2.0-2.15(m,2H)., $^{13}$CNMR($CDCl_3$,400MHz): 134.7,132.7,128.1,114.5, 110.9,

109.3, 107.4, 102.9, 67.3, 30.2, 20.4. IR (KBr) $cm^{-1}$: 3395, 3290, 2980, 1585, 1493, 1450, 1370, 1176, ESI: *m/z* 266 $[M+H]^+$

**6-methyl-2,3,4,9-tetrahydro-1H-carbazol-3-ol (Table-1,entry 12):** Off white solid. m.p. 155-156 $^oC$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ ppm7.7-7.9 (brs,1H),7.05-7.1(d,1H,J=8.0z),6.85-6.95(d,1H,J=8.2Hz),6.75-6.8(s,1H),4.2-4.4(m,1H),3.8-3.9(s,1H), 3.0-3.05(d,1H,5.2Hz),2.6-2.95(m,3H),2.0-2.15(m,2H).; $^{13}$CNMR ($CDCl_3$, 400MHz): 134.7,132.7,129.5, 28.1,110.9,109.3, 107.4, 102.9, 67.3, 30.2, 21.7,20.4.;IR (KBr) $cm^{-1}$: 3385 3215, 2920, 1620, 1448, 1367, 1055, 742; MS (ESI) : *m/z* 202 $[M+H]^+$

**6-Methoxy-2,3,4,9-tetrahydro-1H-carbazol-3-ol (Table-1,entry 13):** Dark brown color solid, m.p. 172-173$^oC$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ ppm 7.7-7.9(brs,1H), 7.22-7.25 (s,1H), 6.85-6.95 (d,2H, J=8.0Hz),4.2-4.4(m,1H), 3.8-3.9(s,1H),3.0-3.05(d,1H,J=5.2Hz),2.6-2.95(m,3H),2.0-2.15(m,2H). 13CNMR (CDCl3 ,400MHz):156.5, 134.7,132.7,128.1,110.9,109.3, 104, 102.9, 67.3, 56, 30.2, 20.4.;IR (KBr) $cm^{-1}$: 3412, 3215, 2920, 1620, 1448, 1367, 1055, 742; MS (ESI) : *m/z* 218 $[M+H]^+$

**3-Hydroxy-2,3,4,9-tetrahydro-1H-carbazole-6-carbonitrile (Table-1,entry 14):** White color solid; m.p. 218-219 $^oC$;$^1$H-NMR (DMSO-$d_6$, 400 MHz) : $\delta$ ppm 11.2-11.5 (brs, 1H), 7.8-7.9 (s, 1H), 7.5(d,2H, J= 8.2Hz), 4.7-4.8 (s, 1H), 3.9- 4.1(m,1H),2.6-3.0(m,2H),2.4-2.5(m,1H), 1.9-2.05(m,1H), 2.7-2.8(m,1H );$^{13}$C NMR (DMSO-$d_6$, 400MHz) : 138, 136.6, 127.2, 123, 122.5, 121, 111.6, 107.7, 99.9, 65.7, 31.1, 29.8, 20.5.;IR (KBr) $cm^{-1}$: 3410, 3226, 2920, 2225, 1625, 1485, 1367, 1050; MS (ESI) :213 [M+H]+

**3-Hydroxy-2,3,4,9-tetrahydro-1H-carbazole-6-carboxamide (Table-1,entry 15):**Dark brown solid, m.p. 183-184 $^oC$; $^1H$ NMR (DMSO-D6, 400 MHz) : $\delta$ ppm11.2-11.3(brs,1H),9.9(brs,1H),8.2-8.3(s,1H),7.8.(s,1H),7.2-7.3(d,2H,J=8.0Hz), 4.7- 4.8 (s, 1H), 3.9-4.1(m,1H), 2.6-3.0 (m,2H), 2.4-2.5(m,1H), 1.9-2.05(m,1H), 2.7- 2.8(m,1H).;IR (KBr) $cm^{-1}$ : 3504, 3291, 2924, 1649, 1473, 1288, 1038.MS (ESI) : *m/z* 231 $[M+H]^+$

**6-Nitro-2, 3,4,9-tetrahydro-1H-carbazol-3-ol(Table-1,entry 16):** Orange color solid, m.p. 200-202 $^0C$; $^1H$ NMR (DMSO-$d_6$, 400 MHz) : $\delta$ 11.8-11.9(brs,1H),8.2-8.3(s,1H),7.85-7.9(d,1H,*J*=8.4Hz),7.7-7.8 (d,1H,J=8.0Hz ),4.7-4.8 (s, 1H ), 4.22-4.1(m,1H), 3.2-3.3(d,1H,J=2.4Hz), 2.7-3.0 (m,3H ), 2.05-2.1(m, 1H), 1.9-2.05(m,1H). IR (KBr) $cm^{-1}$: 3480, 3236, 2902, 1560, 1300, 1068; MS (ESI) : m/z 233 [M+H]+.

**6-Butyl-2,3,4,9-tetrahydro-1H-carbazol-3-ol 4 (Table-1,entry 17) :** Brown solid, m.p. 81-82 $^oC$; $^1H$ NMR ($CDCl_3$, 400 MHz) : $\delta$ ppm7.66-7.8 (s,1H),7.22(s,1H),7.12-7.14(d,1H,J=8.4Hz),6.94-6.96(dd,1H, *J*=1.6,J=7.2Hz),4.2-4.4(m,1H),3.05-3.15(d,1H), 2.62-2.95(m,5H), 2.0-2.15(m,3H), 1.6-1.72(m,2H), 1.35-1.45(m,2H), 0.9-1.0(t,3H). $^{13}$CNMR ($CDCl_3$,400MHz): 134, 133.8, 132.7, 127.7 , 116.8, 110, 106.6, 67.5, 35.7, 34.7, 30.9, 22.3, 13.99; IR (KBr) $cm^{-1}$: 3424, 2922, 1593, 1462, 1327, 867, 771 ; Elemental Analysis: C, 78.87; H, 8.70; N, 5.66; O, 6.67; MS (ESI) : *m/z* 244 $[M+H]^+$

**Spectral data for 2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (Table-2,entry 1):** Yiled:93%; light brown colour solid; m.p. 165-167 $^oC$; $^1H$ NMR (DMSO-$D_6$, 400 MHz): δppm10.71(s,1H),7.28(q,J=7.7 Hz, 2H),6.98(m,1H),6.89(m,1H),3.85(s,2H),3.01(t,J=5.6 Hz,2H), 2.66 (t, J = 5.5 Hz, 2H). $^{13}$C NMR (100 MHz, DMSO-d6): δ 135.4, 133.4, 125.7, 120.1, 118.2, 117.1, 110.7, 108.4, 43.1, 41.8, 24.2. ESI-MS: [M+H]+ = 173.1065 m/z.

**Spectral data for 8-methyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (Table-2,entry 2):** Yiled: 91%; 0ff white colour solid; m.p. 165-166 $^oC$; $^1H$ NMR (DMSO-$D_6$,400 MHz) : 10.9(brs, 1H), 7.25 (s,1H),7.21-7.23 (d, 1H, J=8.4Hz ), 7.07-7.09(d,1H,J=8.0Hz), 3.75-3.9(s,2H),2.9-3.0(t,2H, J=10Hz, 4.8Hz),2.65 (s,2H),2.3(brs,1H);$^{13}$CNMR(DMSO-$D_6$,75MHz):135.2,134.1,128.2, 124, 117.4,112.28,109.3, 108.2,42.8, 41.4, 24.07 ,21.2; Elemental Analysis: C, 76.38; H, 8.58; N, 14.44 (ESI) : *m/z* 187 $[M+H]^+$.

**Spectral data for 8-fluoro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole(Table-2,entry 4):** Yiled:86%;off white colour solid;M.P:142-143$^{o}$C;$^{1}$HNMR(DMSO-$D_6$,400MHz): δppm10.75(brs,1H),7.2-7.3(m,1H),7.02-7.04(dd,1H,J=10Hz,2.4Hz),6.67(m,1H), 3.6(s,2H),3.2-3.3(t,2H,J=11.2Hz,J=5.2Hz),2.64-2.87(t,2H, J=10.8 Hz, J=5.6Hz),2.3-2.4 (brs,1H);$^{13}$CNMR(DMSO-$D_6$,400MHz): 159.4,157.1, 135.2,124.1,117.6, 107, 106.2, 97.1, 46.2, 42.5,32; Elemental Analysis: C, 68.46; H, 5.83; F, 9.79; N, 15.03; ES-MS :m/z 191 [M+H]+.

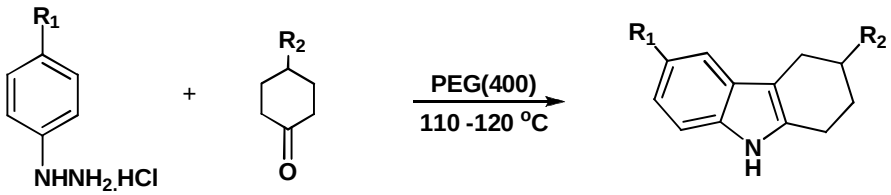
**Spectral data for 8-chloro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b] indole (Table-2,entry 5):**Yiled: 89%; dark brown colour solid; M.P: 133-134$^{0}$C; $^{1}$H NMR (DMSO-$D_6$, 400MHz) : δppm 11.0(brs,1H),7.28-7.44(m,2H),6.97-6.99(d,1H,J=10Hz),3.9-4.4 (m,4H), 3.1 (brs,1H),2.8(s,2H).;$^{13}$CNMR(DMSO-$D_6$,75MHz) :135,133.9, 126.6,122.8,119.9, 116.4, 112.1,41, 40.3,23.6; Elemental Analysis: C,62.93;H,5.36;Cl, 18.15 ;N, 13.55; ES-MS: *m/z* 207.5$[M+H]^{+}$

**Specral data for 8-bromo-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (Table-2,entry 6):**Yiled:88%; brown colour solid ;M.P : 194-195$^{0}$C; $^{1}$H NMR (DMSO-$D_6$, 400 MHz):δppm10.9(brs, 1H), 7.47 (s,1H),7.21-7.23 (d, 1H, J=8.4Hz), 7.07-7.09(d,1H,J=8.0Hz),3.75-3.9(s,2H),2.9-3.0(t,2H, J=10Hz, 4.8Hz),2.65(s,2H);$^{13}$CNMR(DMSO$D_6$,75MHz):135.2,134,127.4,122.28,119.3,112.5,110.6,108.2,42.8,41.4 , 24.07; Elemental Analysis:C,53.61;H,5.42;Br,31.82; N, 12.16 ;ES-MS: *m/z* 251$[M-2H]^{+}$.

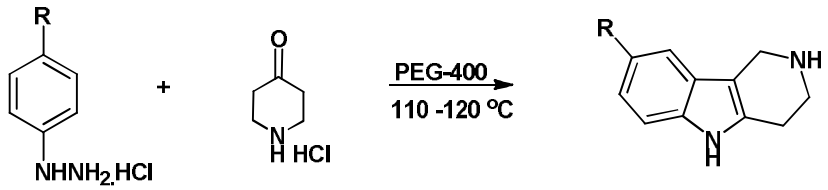
**Spectral data for 8-nitro-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (Table-2,entry 7):**Yiled:86%; orange colour solid; m.p. 220-222$^{0}$C; $^{1}$H NMR (DMSO-$D_6$, 400 MHz): δppm10.65 (brs, 1H), 8.47 (s,1H),8.21-8.23 (d, 1H, J=8.4Hz), 7.77-7.79 (d,1H, J=8.0Hz), 3.75-3.9(s,2H), 2.9-3.0 (t,2H, J=10Hz,4.8Hz),2.65(s,2H);$^{13}$CNMR(DMSO$D_6$,75MHz):144.1,138.3,135.2,134,127.4,119.3,112.5,110.6,42 .8,41.4,24.07; Elemental Analysis: C, 62.82; H, 5.10; N, 18.34; O, 15.73; ES-MS (ESI) : m/z 218 [M+H]+.

## RESULTS AND DISCUSSION

Substituted tetrahydrocarbazoles were synthesized by reacting substituted phenyl hydrazine hydrochlorides(1.0 mmol) with substituted cyclohexanones (1.0 mmol) in Poly Ethylene Glycol at 110-120$^{o}$C(Scheme.1). Similarly tetrahydro-γ-carbolines (Scheme.2) were synthesized by reacting 4-piperdone hydrochloride (1.0 mmol) with substituted cyclohexanones (1.0 mmol) in Poly Ethylene Glycol at 110-120$^{o}$C.




**Scheme 1.** Reaction Scheme for Synthesis of 6-substituted tetra hydro carbazoles.



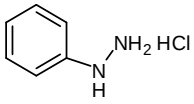
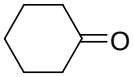
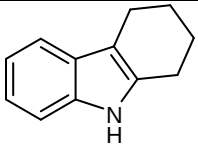
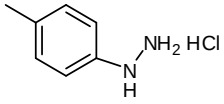
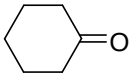
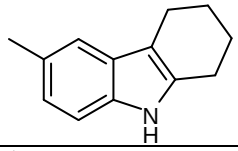
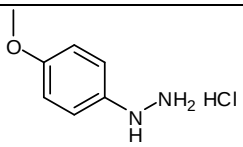
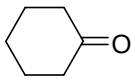
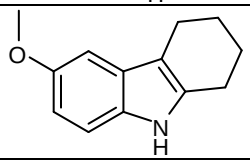
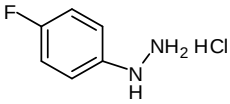
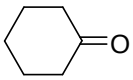
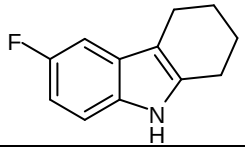
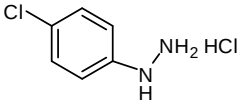
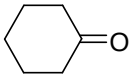
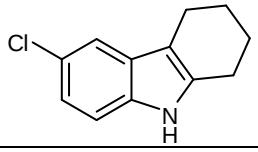
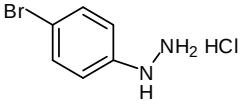
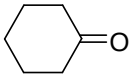
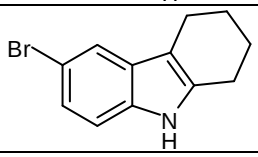

**Scheme 2.** Reaction Scheme for Synthesis of substituted tetra hydro carbolines

In order to optimize the reaction conditions, substituted phenylhydrazine's was treated with varying amounts of cyclohexanone In summary, we have explored an efficient one-pot route to synthesize a series of 1,2,3,4-tetrahydrocarbazoles and γ-carboline or 2,3,4,5-tetrahydro-1H-pyrido[4,3-b] indole from easily available cyclohexanones and 4-piperidone with substituted phenyl hydrazine hydrochloride, using PEG-400 at 110-120$^{o}$C conditions without any other catalysts and acidic reagents. The simple procedures developed , mild reaction conditions used, and shorter reaction times render this method a valuable addition to tetrahydrocarbazole and tetrahydro carboline chemistry.

In the presence of electron releasing groups present at the Para position of phenyl Hydrazine's gave more yield comparatively to the presence of electron withdrawing groups. Low yields observed for preparation of 5-substituted tetrahydrocarbolines and 5-tetrahydrocarbzoles (Table 1,entry 18), for synthesis of 5-substituted tetrahydrocarbolines and 5-tetrahydrocarbzoles we taken 3-substituted hydrazine hydrochlorides are corresponding ketone we get 1:1 ratio of 5 and 7 substituted products because of cyclisation takes place both 5 and 7 positions. This was confirmed by LC-MS.

In the course of our project directed towards the development of new antitumor compounds, we have envisaged the synthesis of new substituted tetrahydrocarbazoles and tetrahydro-γ-carbolines *via* the most widely used green method, the synthesis of substituted tetrahydro carbazol and tetrahydro γ-carboline.proceeds through a [3,3] sigmatropic rearrangement followed by cyclization and elimination of ammonia. This is one of the efficient and economic synthesis of substituted tetrahydrocarbazole and tetrahydro-γ-carboline. Using readily available laboratory reagents with short reaction times under eco-friendly conditions. The product yields are very high ranging between 88-94 % (Table 1,Table 2).

**Table 1:** Synthesis of substituted tetrahydrocarbazole using phenyl hydrazine with cyclohexanone.

| Entry | (1) | (2) | Product (3) | Time(h) | Yield(%)[b] |
|---|---|---|---|---|---|
| 1 |  |  |  | 6 | 93 |
| 2 |  |  |  | 6 | 90 |
| 3 |  |  |  | 5.5 | 90 |
| 4 |  |  |  | 8 | 89 |
| 5 |  |  |  | 8 | 90 |
| 6 |  |  |  | 8 | 91 |

| | | | | | |
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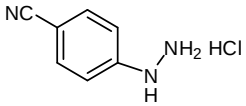
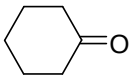
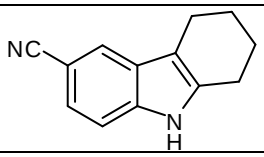
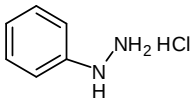
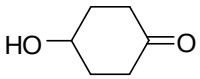
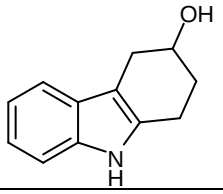
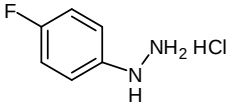
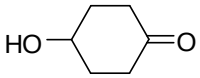
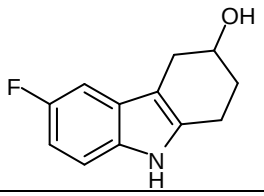
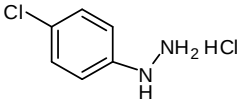
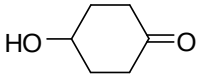
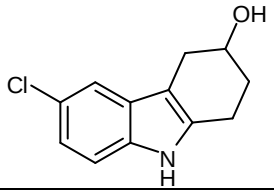
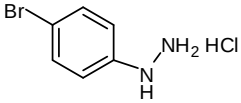
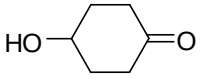
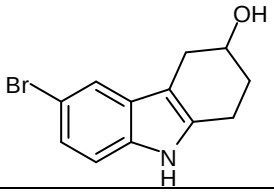
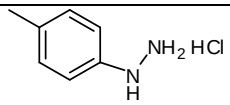
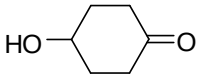
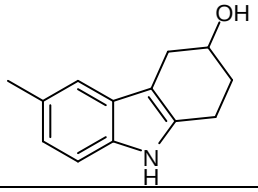
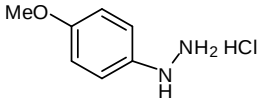
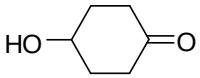
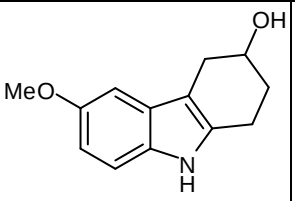
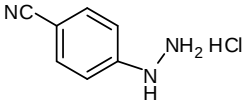
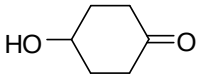
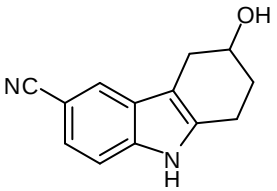
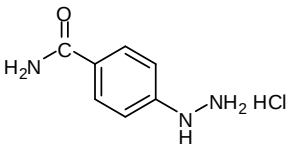
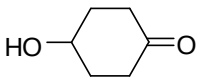
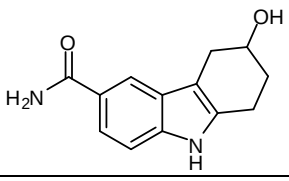
| 7 |  |  |  | 8 | 90 |
| 8 |  |  |  | 6.5 | 92 |
| 9 |  |  |  | 8.5 | 88 |
| 10 |  |  |  | 9 | 88 |
| 11 |  |  |  | 9 | 89 |
| 12 |  |  |  | 7 | 91 |
| 13 |  |  |  | 7 | 89 |
| 14 |  |  |  | 8 | 90 |
| 15 |  |  |  | 9.5 | 88 |

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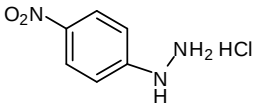
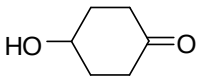
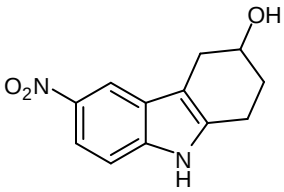
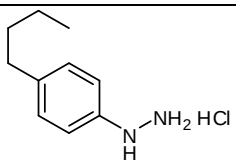
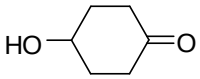
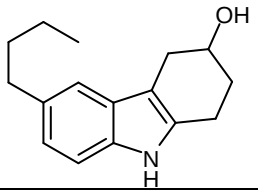
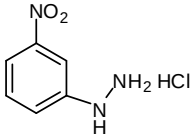
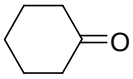
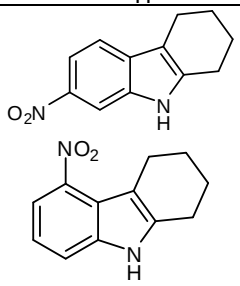
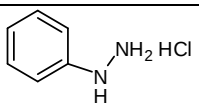
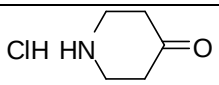
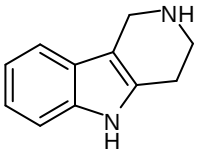
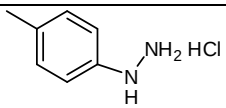
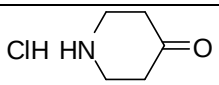
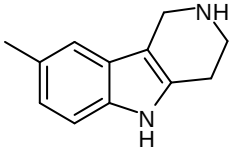
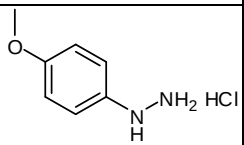
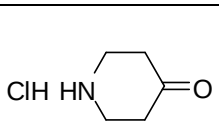
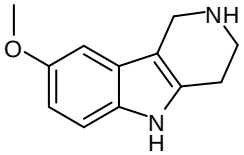
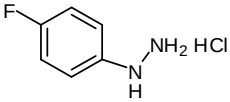
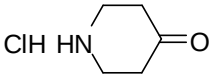
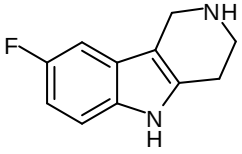
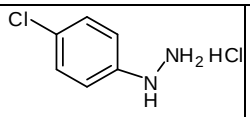
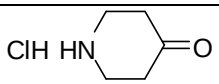
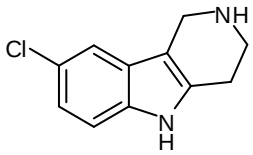
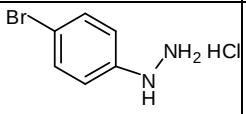
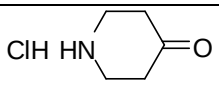
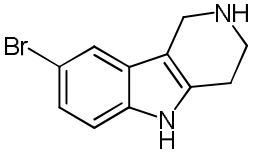
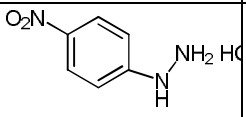
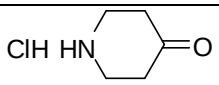
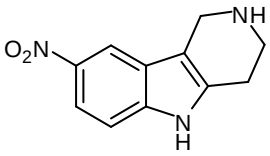
|---|---|---|---|---|---|
| 16 |  |  |  | 8.5 | 90 |
| 17 |  |  |  | 7 | 92 |
| 18 |  |  |  | 9 | 45:45[c] |

[a]**Reaction conditions:** Substituted cyclohexanone (1.0 mmol), phenylhydrazine hydrochloride (1.0 mmol), PEG-400 (5 ml), 110-120 $^{o}$C, 5-10 h. [b]Isolated yield. [c]Ratio of 7 and 5 substitued product by LC-MS.

**Table 2:** Synthesis of substituted tetrahydro carboline using phenyl hydrazine with 4-piperadone.

| Entry | (1) | (2) | Product (3) | Time(h) | Yield(%)[b] |
|---|---|---|---|---|---|
| 1 |  |  |  | 6 | 93 |
| 2 |  |  |  | 6 | 90 |
| 3 |  |  |  | 5.5 | 90 |
| 4 |  |  |  | 8 | 89 |

| | | | | | |
|---|---|---|---|---|---|
| 5 |  |  |  | 9 | 88 |
| 6 |  |  |  | 9 | 89 |
| 7 |  |  |  | 9 | 88 |

[a]**Reaction conditions :** 4-piperidonehydrochloride(1.0mmol),phenylhydrazine hydrochloride (1.0 mmol), PEG-400 (5 ml), 110-120 $^{o}$C, 5-10 h. [b]Isolated yield. [c]Ratio of 7 and 5 substitued product by LC-MS.

All the products were characterized by $^{1}$H, $^{13}$C NMR, and Mass spectra and compared with authentic samples. [19] The reaction is expected to proceed via a two-step sequence with initial phenyl hydrazine are formed corresponding hydrazone with corresponding cyclicketone and the hydrazone cyclised to corresponding tetrahydro carbazol or tetrahydro γ-carboline.

## APPLICATIONS

The developed method is simple and facile and will be a useful addition to green chemistry with an advantage that the reaction excludes hazardous catalysts and highly flammable organic solvents.

## CONCLUSIONS

In conclusion, we have developed an eco-friendly novel protocol for the synthesis of substituted tetrahydro carbazol, tetrahydro γ-carboline in excellent yields under netural conditions by using PEG-400.

## ACKNOWLEDGEMENT

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