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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL MANNICHBASES OF N-SUBSTITUTED TETRAHYDROCARBAZOLE DERIVATIVES

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ABSTRACT

Tetrahydrocarbazole is an important class of heterocyclic compound which plays a vital role in the field of medicinal chemistry. The aim of this research work is to synthesise some novel mannich bases of N-Substituted teterahydrocarbazole derivatives. Teterahydrocarbazole were prepared by fischer indolisation reaction of cyclohexanone with phenylhydrazine in the presence of acetic acid. The mannich bases of these compounds were synthesized by reacting with different aldehydes and P-Aminobenzoic acid. The structures of synthesized derivatives were confirmed by IR, NMR and Mass spectrum. The synthesized compounds were evaluated for antimicrobial activity by cup plate method.

KEYWORDS: Tetrahydrocarbazole, Mannich bases, Antimicrobial activity.

INTRODUCTION

Carbazole skeleton fused with heterocyclic ring have excellent pharmacological activities of their derivatives Carbazole skeleton bearing natural products fused with heterocyclic ring have drawn significant attention due to excellent pharmacological activities of their analogues.[1] There are numerous evidences illustrating that the fused ring of heterocycles at Nth position have gained unique importance on pharmacological studies. Recently, the heterocyclic nitrogen ring system have reported been an excellent anti-microbial activities.[2] Large number of biologically active carbazole derivatives have several pharmacological activities such as antiobesitic, antidiabetic (TypeII diabeties), antipsychotic, anticancer, antimicrobial, antiviral and antiemetic.[3-13] The reaction between a reactive hydrogen atom, an aldehyde and a primary amine (or) secondary amine is called as mannich reaction. Mannich base containing tetrahydrocarbazole derivatives result with high biological activity.

MATERIALS AND METHODS

The melting points were taken in open capillary tube in the electrical melting point apparatus and are corrected. The IR spectra of the compounds were recorded on the FTIR 845 shimadzu IR spectrometer using KBr pellets. ^{1}H NMR spectra were recorded on a Bruker AVANCE 400MHZ spectrometer in DMSO(d-6) & CDCl3 using tetramethylsilane as internal standard. The purity of the compounds was monitered by thin layer chromatography (TLC) on silica-G (Merk) coated glass plates visualised by Iodine chamber.

GENERAL PROCEDURE

STEP I

Synthesis of 1,2,3,4 Tetrahydrocarbazole

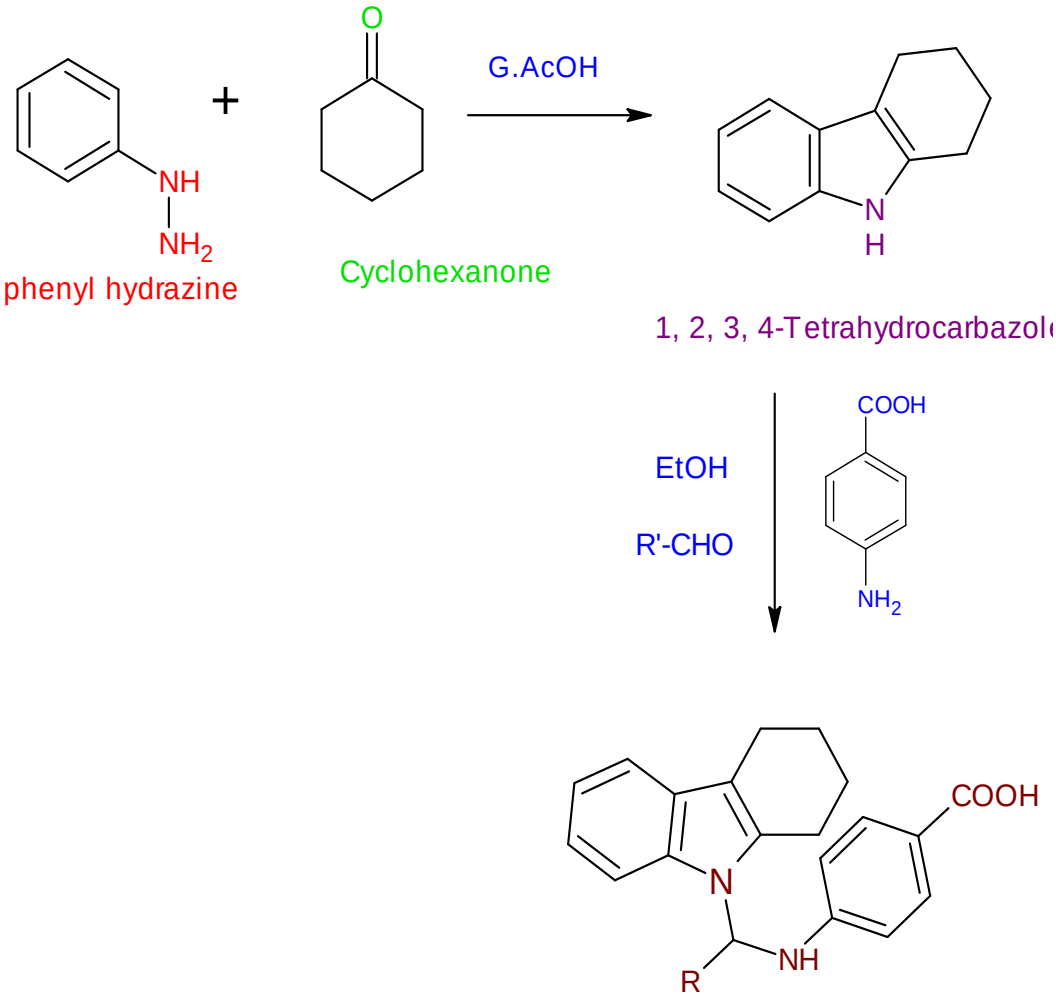
Tetrahydrocarbazole synthesized by an mixture of 0.1 mol of Cyclohexanone and 0.6 mol of Acetic acid contained in a three necked RBF and through dropping funnel 0.1 mol of Phenyl hydrazine is added during 1 hr. After refluxing and stirring an additional hour, the mixture was cooled to 5 °C and filtered. The crude solid was washed with water, recrystallised from ethanol. the purity of the compound were established by single spot on TLC plate. the solvent system was Acetone : DMF (2:1). Melting point were determined in open capillary tubes and were uncorrected.

STEP II

Synthesis of Mannich bases of substituted 1,2,3,4 Tetrahydrocarbazole

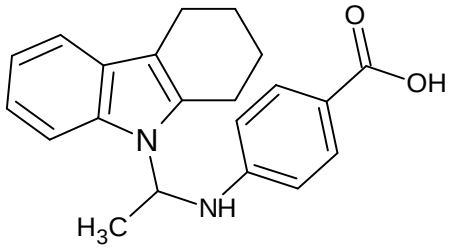
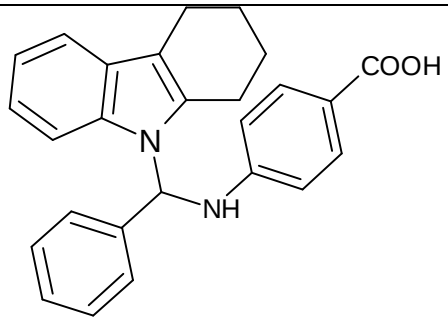
Mannich bases of substituted 1,2,3,4 tetrahydrocarbazole were synthesized as shown by the reaction scheme. 1,2,3,4 tetrahydrocarbazole (0.01 mole) in 30 mL ethanol, Para amino benzoic acid (0.01 mole) and Different substituted Aldehydes (1 mL) was refluxed for 3-4 h. On cooling the reaction mixture was poured on crushed ice. The precipitated mannich base was filtered and recrystalized from ethanol. The purity of the compound was established by single spot inTLC plate (silica gel).

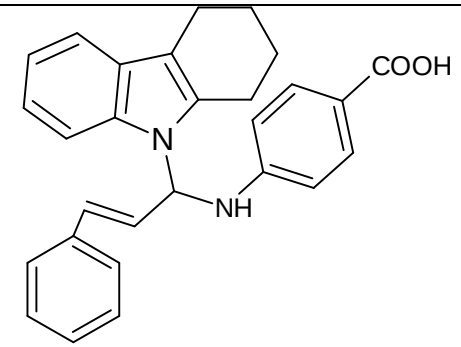
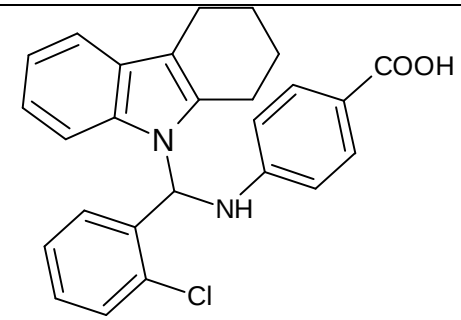
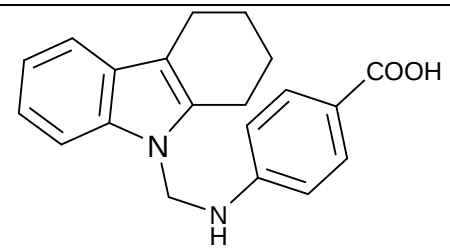
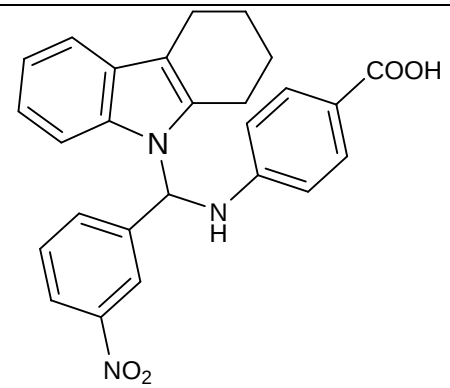
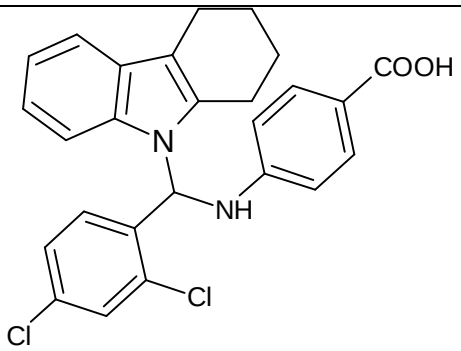
EXPERIMENTAL WORK
SCHEME

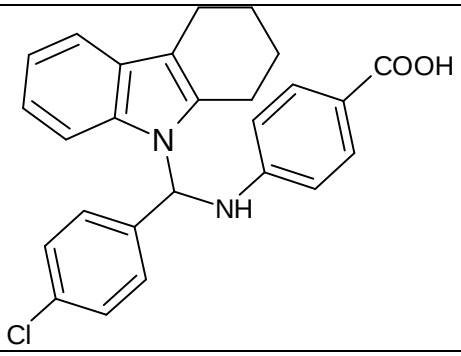


4-[(1,2,3,4-tetrahydro-9*H*-carbazol – 9-ylmethyl)amino]benzoic acid

RESULTS AND DISCUSSION
DIFFERENT TYPES OF ALDEHYDES

S.No	Compoud Code.	Chemical Structure	Molecular Formula	Molecular Weight	Yield (%)	Melting Point	R_f value
1	D1		$C_{21}H_{24}N_2O_2$	336	75%	129^{O}C	0.78
2	D2		$C_{26}H_{26}N_2O_2$	398	68%	137^{O}C	0.84

3	D3		$C_{28}H_{28}N_2O_2$	424	70%	139^{O}C	0.78
4	D4		$C_{26}H_{25}N_2O_2Cl$	397	78%	124^{O}C	0.93
5	D5		$C_{20}H_{22}N_2O_2$	336	75%	158^{O}C	0.87
6	D6		$C_{26}H_{24}N_3O_4$	440	62%	174^{O}C	0.88
7	D7		$C_{26}H_{24}N_2O_2Cl_2$	468	55%	142^{O}C	0.75

8	D8		$C_{26}H_{25}N_2O_2Cl$	433	72%	184^OC	0.79

D1- 4-(1-(5,6,7,8-tetrahydrocarbazole-9-yl)ethylamino)benzoic acid
N-H(str)- 3739.05, C-H(str)- 3395.64, C=C(str)- 1574.75, C-O(str)- 1319.31H[1] NMR: 6.93(d,Ar-H),4.64(s,CH),2.3(s,CH_3) 1H-NMR (DMSO)(d/ppm) 1.045 – 1.245 (m,8H,-CH2 Cyclo), 2.335 (s,1H,-CH2), 4.712 (s,1H,-CS-NH) Mass spectroscopy data: m/z 395.3 (M+)

D2- 4-(phenyl(5,6,7,8-tetrahydrocarbazole-9-yl)methylamino)benzoic acid
C=O(str)- 1681.93, N-H(str)- 3738.05, C-H(str)- 3396.64, C=C(str)- 1593.20 C-C(bending)- 1085.92. 1H-NMR (DMSO)(d/ppm) δ 1.112 – 1.549 (m,8H,-CH2 Cyclo), δ 2..534 (s,1H,-CH2), δ 3.843 (s,1H,Ar-CH=N), δ 4.503 (s,1H,-CS-NH), δ 7.131-7.931(m,8H,Ar-H), Mass spectroscopy data: m/z 434.1(M+).

D3- (E)-4-(3-phenyl-1-(5,6,7,8-tetrahydrocarbazole-9-yl)allylamino)benzoic acid 9C-H(str)-3398.57, O-H(str)-2530.07, C-C(str)-1284.59, C-O-1174.65, C=O(stretching)-1674.21. 1H-NMR (DMSO)(d/ppm) δ 1.079 – 1.193 (m,8H,-CH2 Cyclo), δ 2.506 (s,1H,-CH2), δ 3.402 (s,3H,-OCH3), δ 4.716 (s,1H,-CS-NH),), Mass spectroscopy data: m/z 421.2 (M+).

D4-4-(2-chlorophenyl)(5,6,7,8-tetrahydrocarbazole-9-yl)methylamino)benzoic acid
C-H(str)- 3398.57, C-H(Aro)- 733.74, C-N(str)- 1448.54, C=C(str)- 1234.44, C-N(str)- 3398.57. 1H-NMR (DMSO)(d/ppm) δ 1.066 – 1.431 (m,8H,-CH2 Cyclo), δ 2.506 (s,1H,-CH2), δ 3.679 (s,1H,Ar-CH=N), Mass spectroscopy data: m/z 417.2 (M+).

D5-4-((5,6,7,8-tetrahydrocarbazole-9-yl)methylamino)benzoic acid
C-H(str)-3390.72, C-H(Aro)- 740.67,C-C(str)- 1286.52, O-H(str)- 2512.07, C-O - 1172.72. 1H-NMR (DMSO)(d/ppm) 1.126 – 1.339 (m,8H,-CH2 Cyclo), δ 2.506 (s,1H,-CH2), δ 3.524 (s,1H,Ar-CH=N), δ 4.033 (s,1H,-CS-NH), δ 7.333-7.622 (m,8H,Ar-H), Mass spectroscopy data: m/z 381.3(M+).

D6-4-(3-nitrophenyl)(5,6,7,8-tetrahydrocarbazole-9-yl)methylamino)benzoic acid
C-H(str)- 3396.64, C-C(str)- 1365.60, C-C(Aro)- 817.82, C-O(bending)- 1166.98, C=O(stretching)- 1678.07. 1H-NMR (DMSO)(d/ppm) δ 1.124 – 1.242 (m,8H,-CH2 Cyclo), δ 2.506 (s,1H,-CH2), δ 3.175 (s,1H,Ar-CH=N), δ 4.529 (s,1H,-CS-NH), Mass spectroscopy data: m/z 382.3(M+).

D7-4-(2,4-dichlorophenyl)(5,6,7,8-tetrahydrocarbazole-9-yl)m ethylamino)benzoic acid
C-H(str)- 3396.64, C=C(str)- 1591.27, C-N(str)- 1423.47, C=O(bending)- 1168.85, N-H(stretching)- 3739.66. 1H-NMR (DMSO)(d/ppm) δ 1.120 – 1.245 (m,8H,-CH2 Cyclo), δ 2.506 (s,1H,-CH2), δ 3.234 (s,1H,Ar-CH=N), δ 4.226 (s,1H,-CS-NH), Mass spectroscopy data: m/z 385.1(M+).

D8-4-((4-chlorophenyl)(5,6,7,8-tetrahydrocarbazole-9-yl)mthylamino)benzoic acid
C-H(stretching)- 3335.07, C=C(stretching)- 1581.63, N-H(stretching)- 3752.21, C-H(Aromatic)- 723.31, C-O(stretching)- 1346.31. 1H-NMR (DMSO)(d/ppm) δ 1.110 – 1.509 (m,8H,-CH2 Cyclo), δ 2.698 (s,1H,-CH2), δ 3.734 (s,1H,Ar-CH=N), δ 4.567 (s,1H,-CS-NH), δ 7.123-7.890 (m,8H,Ar-H), Mass spectroscopy data: m/z 445.1(M+).

Antibacterial activity
The synthesised compounds were subjected to antimicrobial screening by cup plate method for zone of inhibition. The Antibacterial activity was tested against various gram positive and gram negative bacteria. The zone of inhibition was compared with the standard drug ciprofloxacin using Dimethyl formamide as solvent control.

Table No. 2: Antimicrobial activity of synthesized compounds.

Comp 100(µg/ml)	Zone of inhibition(mm)			
	Gram Positive		Gram negative	
	B.Subtilis	S.auregonosa	K.Pneumonia	E.coli
D1	17	15	19	15
D2	14	18	19	17
D3	18	17	15	18
D4	22	16	18	14
D5	24	17	17	18
D6	18	20	16	15
D7	19	18	17	20
D8	18	19	18	16
Std ciprofloxacin Drug 100(µg/ml)	26	22	20	24
Solvent Control(DMSO)	-	-	-	-

CONCLUSION

In conclusion, we have developed a novel protocol for high yielding method for the synthesis of some novel mannich bases of N-substituted tetrahydrocarbazole derivative. This methodology can be used for the synthesis of various carbazole skeletons with the required substituents. All the synthesized compounds have been confirmed by various spectral techniques viz FTIR, 1H NMR, 13C NMR and mass spectroscopy. The present work deals with the effective anti bacterial activity of tetrahydrocarbazole derivatives(D4,D5,D7). The synthesized compounds found to have good antibacterial activity.

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