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An Efficient Synthesis of Bromoacetyl Derivatives of Bridged Carbazoles With Antibacterial Activity

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Abstract

Heterocyclic ring system of tetrahydrocarbazole and their derivatives aroused great interest for the past and recent years owing to broad diversity of Pharmaceutical applications. A number of biologically active carbazole derivatives are of interest as drug-like templates. Compound **A** 1-bromoacetyl-1,2,3,4-tetrahydrocarbazole have been synthesized using bromoacetylbromide with 1,2,3,4-tetrahydro carbazole in dimethylformamide as a solvent. 1-bromoacetyl-1,2,3,4-tetrahydrocyclopenta[b] indole **B** and compound **C 5**-bromoacetyl-5,6-dihydrobenzo[α]carbazole have also been synthesized by similar procedure as mentioned above. The synthesized organic carbazole derivatives have been confirmed using FTIR, ^{1}HNMR, ^{13}CNMR and MASS Spectroscopy. Evaluation of antibacterial activity were examined for synthesized carbazole derivatives, the result show that the bromoacetyl derivative of carbazole found to have good antibacterial activity.

Keywords

Bromoacetylbromide, 1-bromoacetyl-1,2,3,4-tetrahydrocarbazole, Dimethyl formamide, 1,2,3,4-tetrahydrocyclo[b]indole, Ciprofloxacin.

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INTRODUCTION

Heterocyclic compounds participate an imperative role in the metabolism of living cell. A number of the heterocyclic compounds have microbial activity and medicinal uses. The chemistry of heterocyclic compounds has desire to study of long time. Especially nitrogen containing heterocyclic compounds have received unique attention in pharmaceutical chemistry due to their varied medicinal potential.[1] Heterocyclic compounds containing nitrogen, sulphur and oxygen moieties compose the nucleus structure of a number of biologically interested compounds, against bacteria and fungi. [2] Structurally unique and functionality enriched heterocyclic systems are of great significances in chemically and biologically related research areas. [3] Heterocyclic compounds are widely distributed in nature and occupy a prominent place in medicinal chemistry as pharmaceuticals and drug intermediates. Tetrahydrocarbazole was nitrogen containing heterocyclic compound and it's found to be a starting

material for the synthesis of larger number of pharmacophores [4] Nitrogen containing heterocyclic such as indole or carbazole are probably the most widely spread nitrogen heterocycles in nature. [5] The fused heterocycles with the carbazole skeletons are also proficient for their medicinal activities. Obviously from the literature that the derivatives of carbazole moiety possess a extensive field of pharmacological activities, such as antibacterial [6–8] antifungal, [9,10] antitumour, antineoplastic,[11–15] anticonvulsant,[16] antioxidant,[17] antidiabetic, [18] antipsychotic[19] and larvicidal activity.[20] Various hetero annulated carbazole derivatives have drawn interest because of their natural occurrence and the broad spectrum of biological activity associated with these compounds.

Some of indole alkaloids possess aza-cyclo alkano (b) indole structures. For example, such alkaloids as eseroline and physostigmine are based on the pyrrolo (2,3-b) indole unit, while the highly promising anti cancer agent echitamine.[21] Cyclopenta(b)indole derivative were used for the treatment and prevention of central nervous system disorders as well as obsessive – compulsive disorder, depression, anxiety, generalized anxiety disorder. Above derivative also cures the schizophrenia, panic disorder, migraine, sleep disorders (sleep apnea), eating disorders (hyperphagia), obesity, epilepsy and spinal cord injury. The scope of present work is to synthesis bridged carbazole derivatives an enhanced Fischer's synthesis and antimicrobial evaluation.

EXPERIMENTAL

Synthesis of bromoacetylcarbazole derivatives have been carried out using the chemicals Cyclohexanone, Cyclopentanone, Alpha-tetralone, Phenylhydrazine Bromoactylbromide and Dimethyl formamide were purchased from Merck.

The melting points of synthesized compounds were resolute by open capillary tubes by an X-5A Melting point equipment and were uncorrected. FTIR spectra was recorded on a Alpha Bruker FTIR Spectrometer with KBr pellets. The 1H NMR Spectra were deliberate on a Bruker proton NMR-Avance 400 MHz with chemical shift expressed in ppm downlfield from TMS as internal reference in DMSO(d-6). The 13C NMR Spectra were found at 400 MHz with a Bruker Avance Spectrometer. Mass Spectra were recorded on GC-MASS Spectrometer with methanol.

SYNTHESIS OF 1-BROMOACETYL-1,2,3,4-TETRAHYDRO CABAZOLE

Equimolar quantities of 1,2,3,4-tetrahydrocarbazole (0.01mol) and bromoacetyl bromide (0.01mol) in dry dimethylformamide were taken in round bottom flask fitted with condenser with catalytic amount of potassium carbonate. The content was refluxed for overnight with constant stirring. After the completion of reaction with the help of thin layer chromatography, the reaction mixture poured into ice cold water. The obtained product was filtered and recrystallised using ethanol.

Yield :96%, Melting point 120-122°C, FTIR (KBr) :3380cm-1(N-H), 2910, 2832cm-1(C-H aliphatic), 1755 cm-1 (C=O), 745 cm-1(C-C). 1H NMR (DMSO d6, ppm): 10.62 (S, N-H), 6.88-8.12 ppm (aromatic protons) ,1.80-1.84 (m,2H), 2.50-2.13 ppm (2H, m), 2.63-2.69 ppm(H, t), 3.34ppm(2H,S). 13C NMR (DMSO d6): 111-149 ppm,177 ppm (C=O), 68, 75 & 20-29 ppm (aliphatic carbons). Mass spectrum: m/e ratio 294.1, 296.2 (M+2).

SYNTHESIS OF 1-BROMOACETYL-1,2,3,4-TETRAHYDROCYCLO PENTA[B]INDOLE

About 0.01mol of 1,2,3,4-tetrahydrocyclopenta[b]idole with bromoacetyl bromide (0.01mol) were taken in round bottom flask in dry dimethylformamide with a pinch of potassium carbonate. The reaction mixture was refluxed for overnight with continuous stirring. After the completion of reaction, the content was poured into ice cold water. The product formed was filtered and recrystallised with ethanol.

Yield: 98 %, Melting point 216-218°C, FTIR(KBr): 3450cm-1(N-H), 2950, 2825cm-1(C-H aliphatic), 1750 cm-1 (C=O), 750 cm-1(C-C). 1H NMR (DMSO d6, ppm): 8.37 (S, N-H), 7.22-7.44 ppm (aromatic protons), 2.70-2.74 ppm (2H, m), 2.15-2.19 ppm(2H, t), 3.09-3.11ppm (H, d) , 4.61 ppm(2H,S). 13C NMR (DMSO d6): 104-142 ppm,172 ppm (C=O), 62 & 23-29 ppm (aliphatic carbons). Mass spectrum: m/e ratio 262.9, 264.02 (M+2).

SYNTHESIS OF 5-BROMOACETYL-5,6-DIHYDRO-11H-BENZO[A] CARBAZOLE

The 5,6-dihydro-11H-benzo[α]carbazole (0.01mol) and bromoacetyl bromide (0.01mol) in dry dimethylformamide with catalytic amount of potassium carbonate were taken in round bottom flask fitted with condenser. The content was refluxed with steady stirring for overnight. After the completion of reaction using thin layer chromatography, the reaction mixture

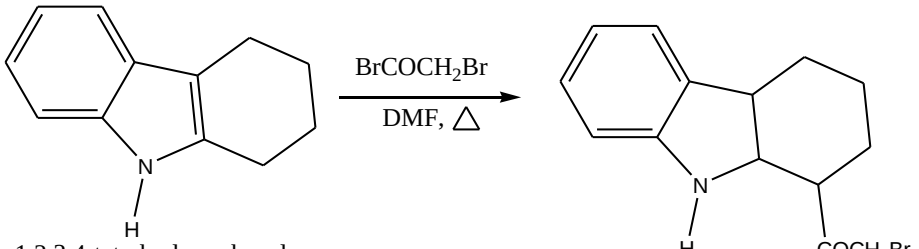
poured into ice cold water. The synthesized product was filtered and recrystallised by ethanol.

Yield :82%, Melting point 90°C, FTIR(KBr) :3400cm-1(N-H), 2975, 2830 cm-1(C-H aliphatic), 1745 cm-1 (C=O), 800 cm-1(C-C). 1H NMR (DMSO d6, ppm): 12.22 (S, N-H) , 7.22-8.69 ppm (aromatic protons) ,1.11-1.17 (d ,2H), 2.51-2.54 ppm (H, t), 3.40 ppm(2H,S). 13C NMR (DMSO d6): 111-139 ppm,173 ppm (C=O), 50 & 29 ppm (aliphatic carbons). Mass spectrum: m/e ratio 349.08, 351.02 (M+2).

EVALUATION OF ANTIBACTERIAL ACTIVITIES

AGAR WELL DIFFUSION METHOD

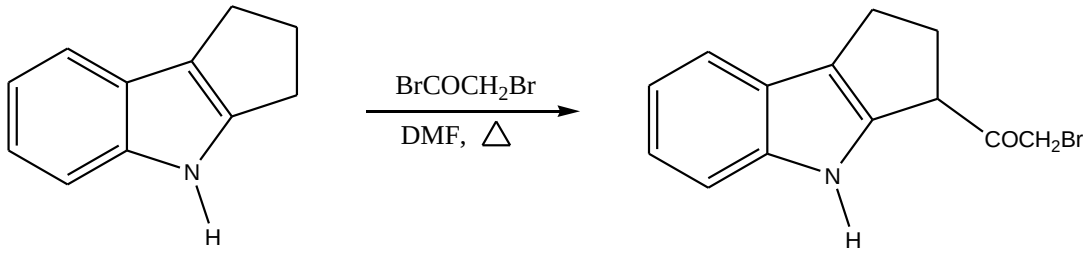
Antimicrobial analysis was followed with standard agar well diffusion method to swot up the antibacterial activity of compounds. The test organisms were flood-inoculated onto the surface of BHI agar and then dried. Five-millimeter diameter wells were cut from the agar by a sterile cork-borer and 30 µL of the sample solution were poured into the wells. The plates were incubated for 18 h at 37°C for bacteria. Antibacterial activity was evaluated by measuring the diameter of the zone of inhibition in mm against the test microorganisms. DMSO was used as solvent control. Ciprofloxacin was used as reference antibacterial agent. The tests were carried out in triplicate. Upon incubation the zone of clearance around the wells were measured. The zone of inhibition diameter in mm as calculated



1,2,3,4-tetrahydrocarbazole

1-bromoacetyl-1,2,3,4-tetrahydrocarbazole

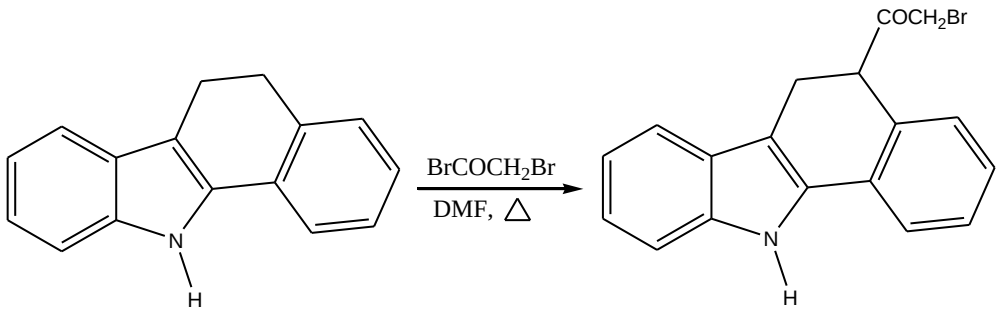
SCHEME 1.



1,2,3,4-tetrahydrocyclopenta[b]indole

1-bromoacetyl-1,2,3,4-tetrahydrocyclopenta[b]indole

SCHEME 2.



5,6-dihydro-11H-benzo[a]carbazole

5-bromoacetyl-5,6-dihydro-11H-benzo[a]carbazole

SCHEME 3.

RESULT AND DISSCUSSION

1-BROMOACETYL-1,2,3,4-TETRAHYDROCABAZOLE

The [b]carbazole derivatives were synthesised by Fischer indole synthesis of derivative of cyclohexanone

with phenyl hydrazine followed by bromoacetylation to yield compound **A**. The FTIR spectrum of the compound **A** (**Fig 1**) was denote the medium intensity band at 3380 cm^{-1} corresponds to the N-H stretching vibration. The sharp band appeared at 2910 and 2832 were assigned to the aliphatic C-H stretching vibration. In **Fig 2** ^{1}NMR spectrum a singlet at 10.62 δ was due to N-H proton. The chemical shift value at 6.88-8.12 δ equivalent to aromatic protons. The δ value appeared at 1.8-2.69 δ corresponds to aliphatic protons. ^{13}C NMR (DMSO d^{6}) (**Fig 3**) The peak appeared at 177 ppm corresponds to the carbonyl carbon. The spectral value111-149 ppm corresponds to aromatic carbons. The aliphatic carbon atoms had shown the spectral peak at 20-29 ppm, 68 ppm and 75 ppm. Mass spectrum : m/e ratio 294.1, 296.2 (M+2) have shown in **Fig 4**.

1-BROMOACETYL-1,2,3,4-TETRAHYDROCYCLOPENTA[B]INDOLE

The FTIR spectrum (**Fig 5**) was attributed to the band present at 3450cm^{-1} have been assigned to N-H stretching vibration. The band appeared at 2950, 2825cm^{-1} was associated with aliphatic C-H stretching vibration. In the ^{1}H NMR spectrum a singlet at 8.37 ppm was due to N-H proton. For aromatic protons the multiplet signal appeared at 7.22 ppm-7.44ppm .The alicyclic protons appeared at 2.15-3..11 ppm. The singlet peak at 4.61 ppm corresponds to the proton neighbouring to carbonyl group presented in **Fig 6**. In the ^{13}C NMR (DMSO d^{6}) predicts that the carbon atom present neighbouring to nitrogen atom has spectral value at 142 ppm. The spectral value104-140 ppm corresponds to aromatic carbons have shown in **Fig 7.** The aliphatic carbon atoms had shown the spectral peak at 23-29 ppm. The spectral value 62 ppm corresponds to the carbon adjacent carbonyl group. From the spectra (**Fig 8**) the molecular ion peak of the compound was observed m/e ratio 262.9, 264.02 (M+2).

5-BROMOACETYL-5,6-DIHYDRO-11H-BENZO[A]CARBAZOLE

The FTIR spectrum (**Fig 9**) of 5-bromoacetyl-5,6-dihydro-11H-benzo[α]carbazole shows that the sharp intensity band at 3400 cm^{-1} was observed due to the N-H stretching vibration. The sharp band appeared at 2975 cm^{-1} and 2830 cm^{-1} associated with aliphatic C-H stretching vibration. The peak at 1745 cm^{-1} was associated the C=O stretching vibration.In the **Fig 10** ^{1}H NMR spectrum of compound **C** shows that the chemical shift at 12.22 ppm was attributed to the N-H proton. The aromatic protons attributed at 7.22-8.69 ppm and the siglet signal for two protons appeared at 3.40 ppm were attributed to the aliphatic protons. In the ^{13}C NMR spectrum of compound **C** have shown in **Fig 11**, the signals appeared in the range 111 ppm-139 ppm was attributed to the aromatic carbons. The chemical shift value 50 ppm and 173 ppm corresponds to the carbon present neighbouring to carbonyl group and carbonyl group. The molecular ion peak of the compound **C** was observed m/e ratio 349.08, 351.02 (M+2) in **Fig 12**. This was good agreement with in the theoretical value.

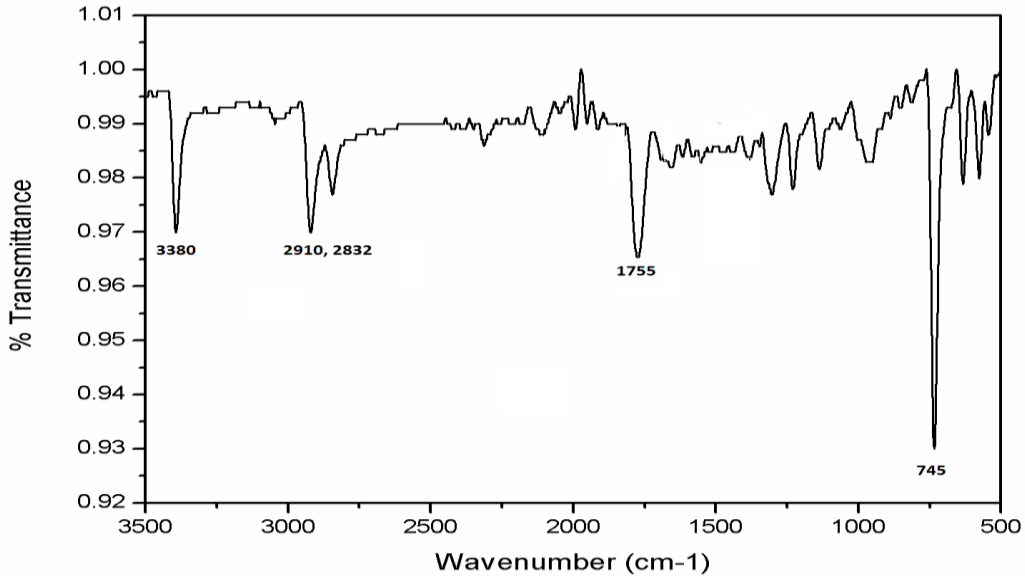


Figure 1. FT-IR Spectrum of 1-bromoacetyl-1,2,3,4-tetrahydrocarbazole.

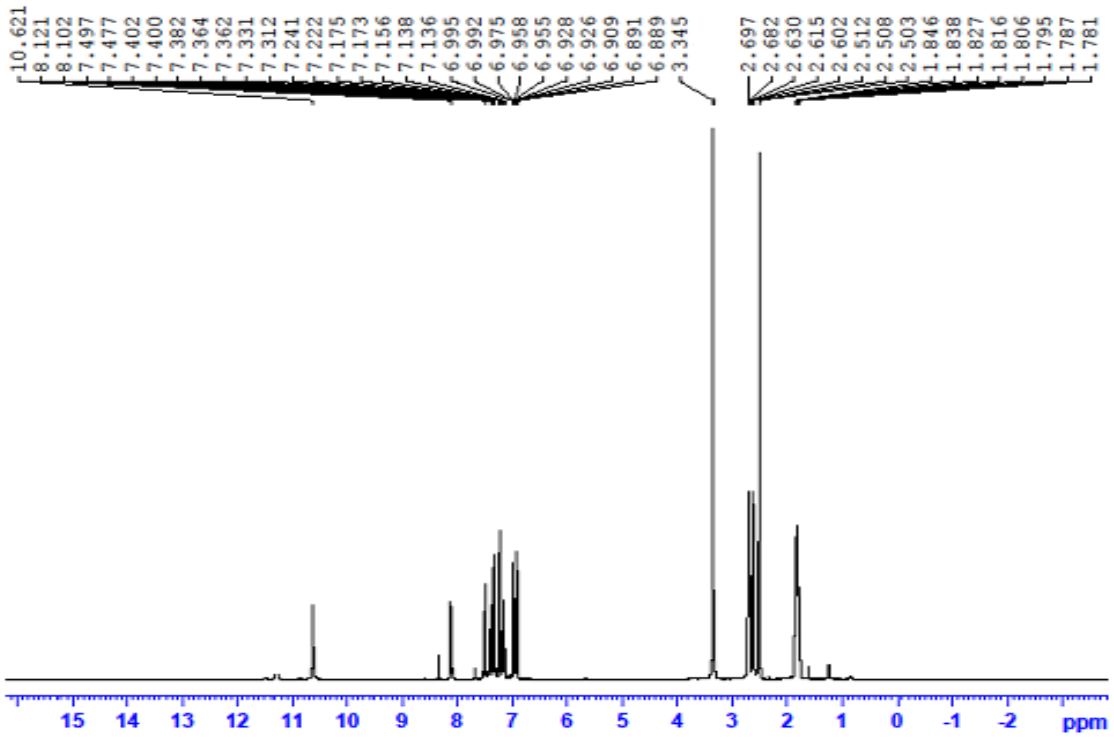


Figure 2. ^{1}H NMR Spectrum of 1-bromoacetyl-1,2,3,4-tetrahydrocarbazole

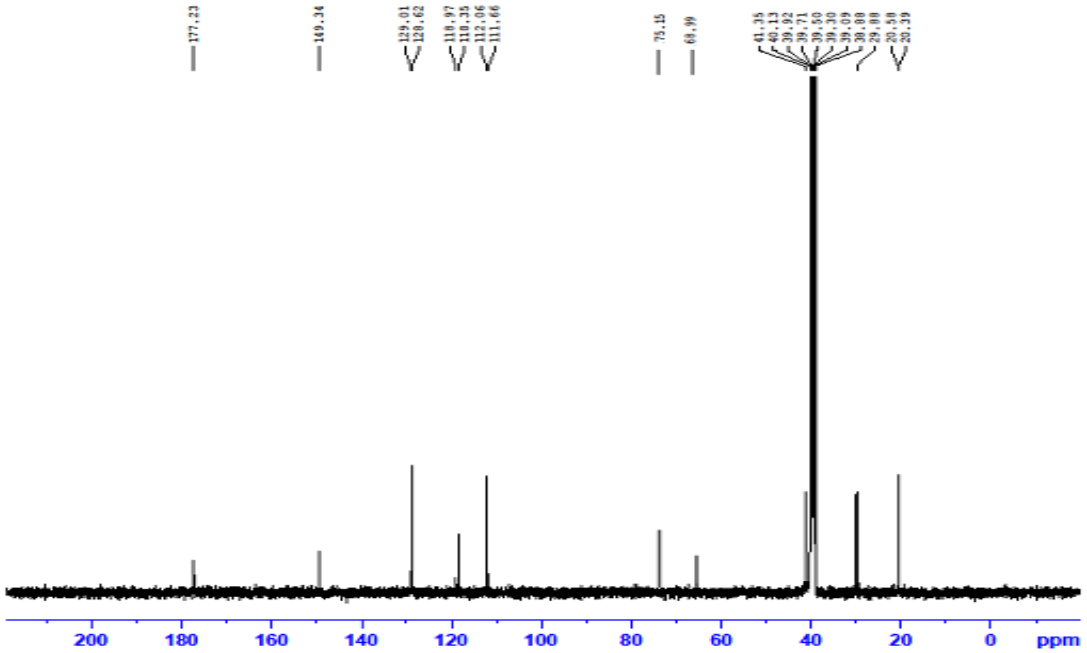


Figure 3. ^{13}C NMR Spectrum of 1-bromoacetyl-1,2,3,4-tetrahydrocarbazole

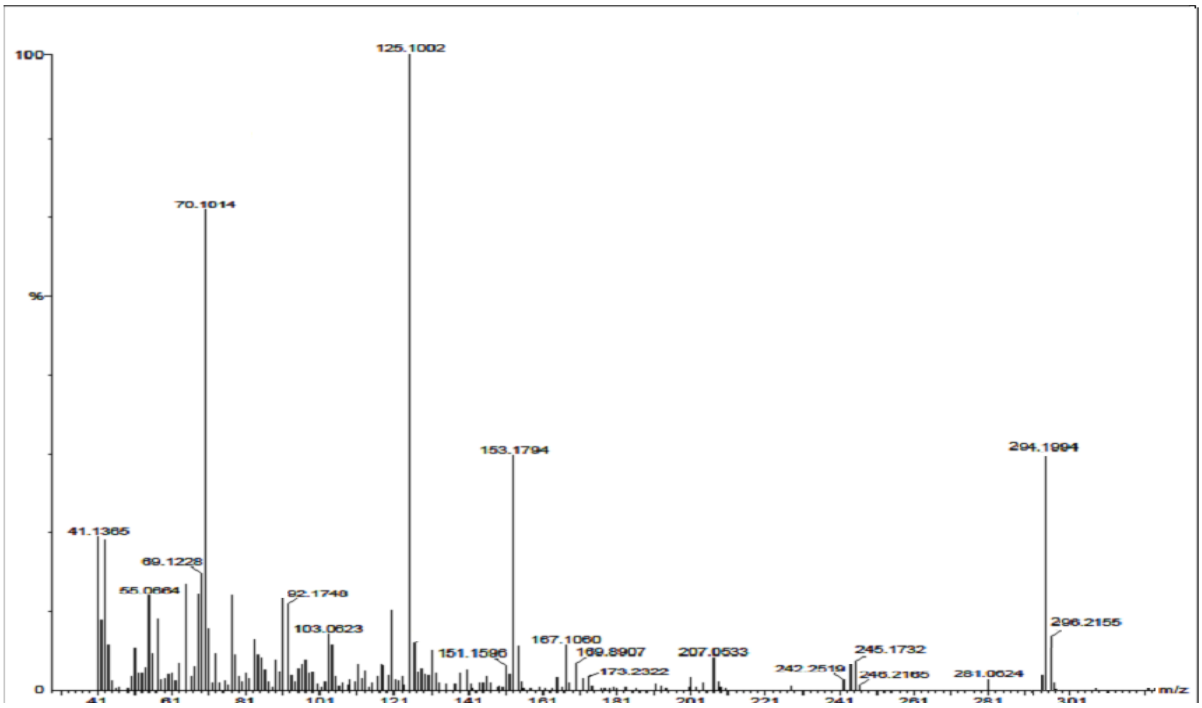


Figure 4. GC MASS Spectrum of 1-bromoacetyl-1,2,3,4-tetrahydrocarbazole

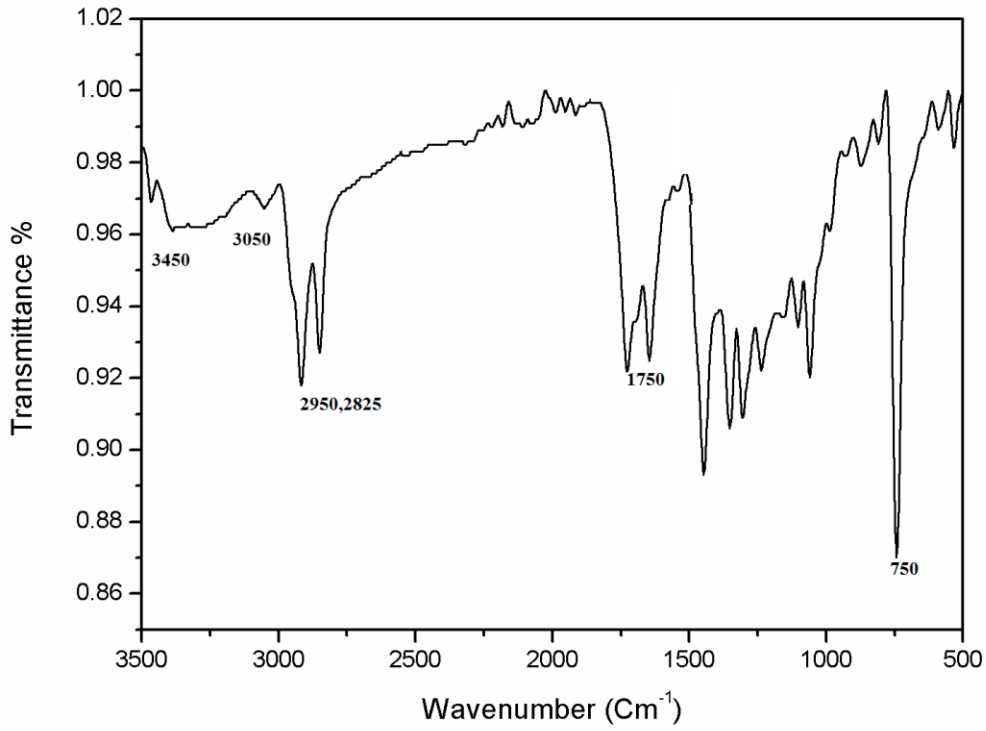


Figure 5. ^{1}H NMR Spectrum of 1-bromoacetyl -1,2,3,4-tetrahydrocyclopenta[b] indole.

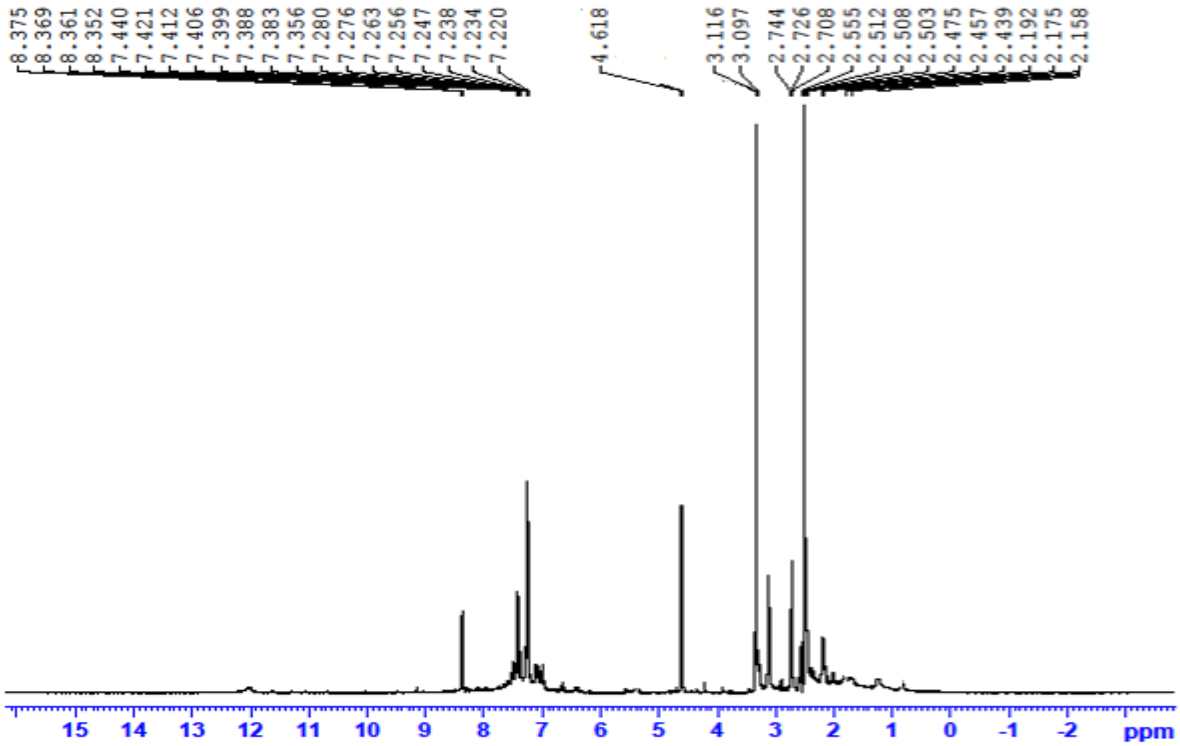


Figure 6. ^{1}H NMR Spectrum of 1-bromoacetyl -1,2,3,4-tetrahydrocyclopenta[b] indole.

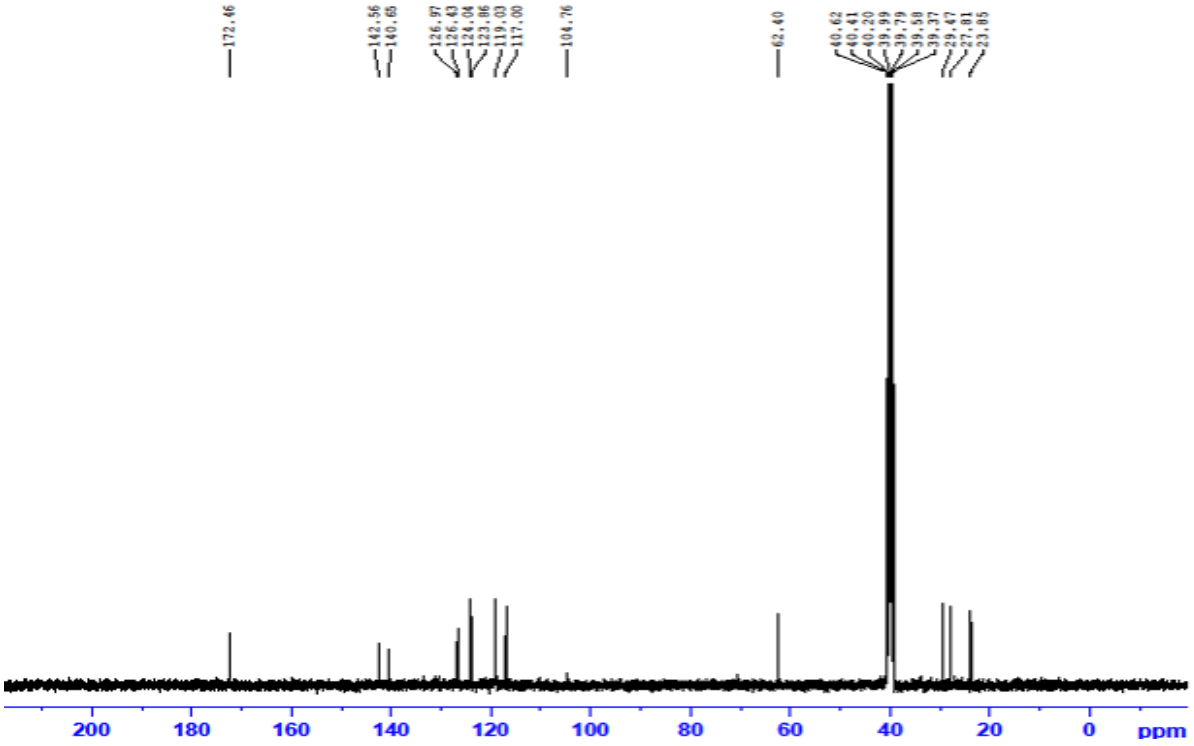


Figure 7. ^{13}C NMR Spectrum of 1-bromoacetyl -1,2,3,4-tetrahydrocyclopenta[b]indole.

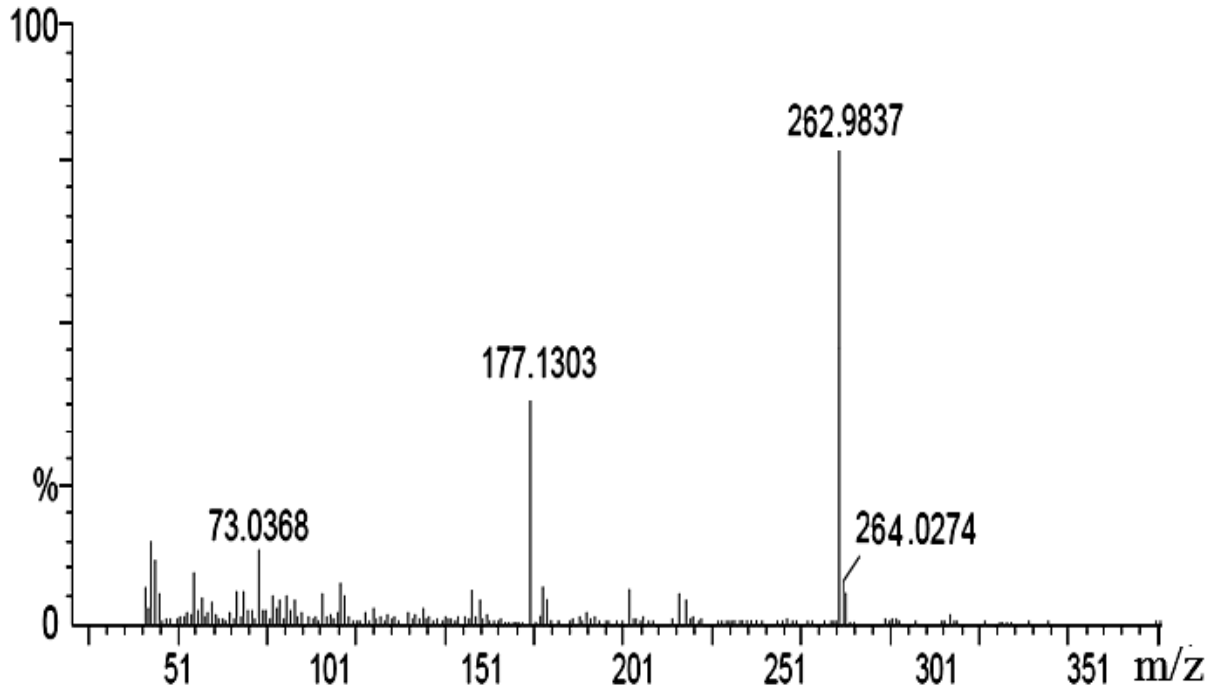


Figure 8. GC Mass Spectrum of 1-bromoacetyl -1,2,3,4-tetrahydrocyclopenta[b]indole.

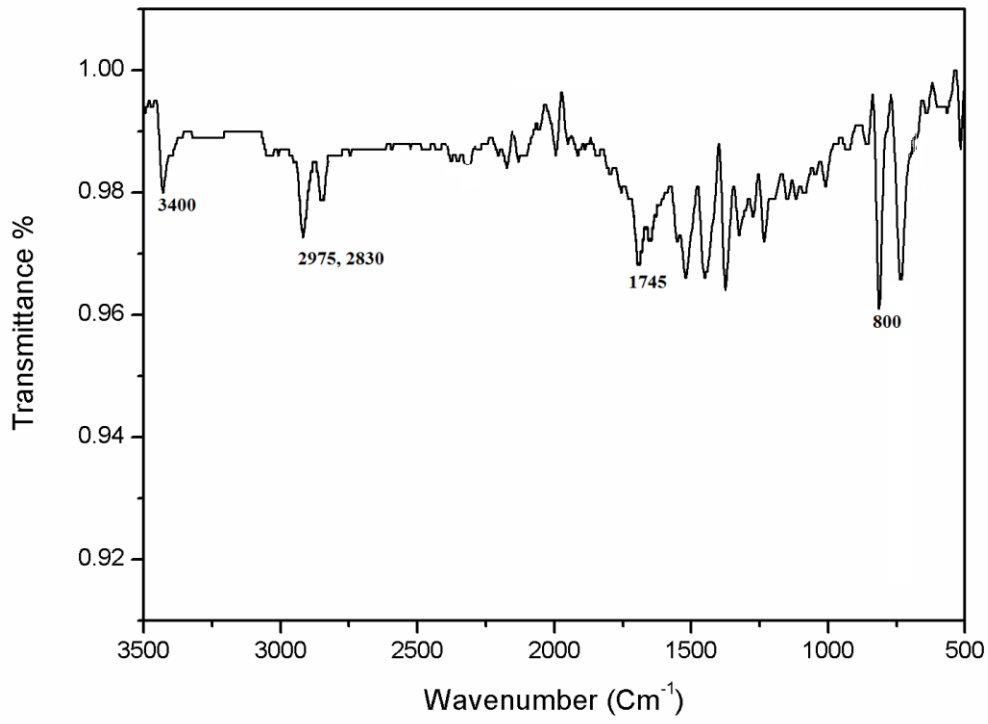


Figure 9. ^{1}H NMR Spectrum of 5-bromoacetyl -5,6-dihydro-11H-benzo[α]carbazole.

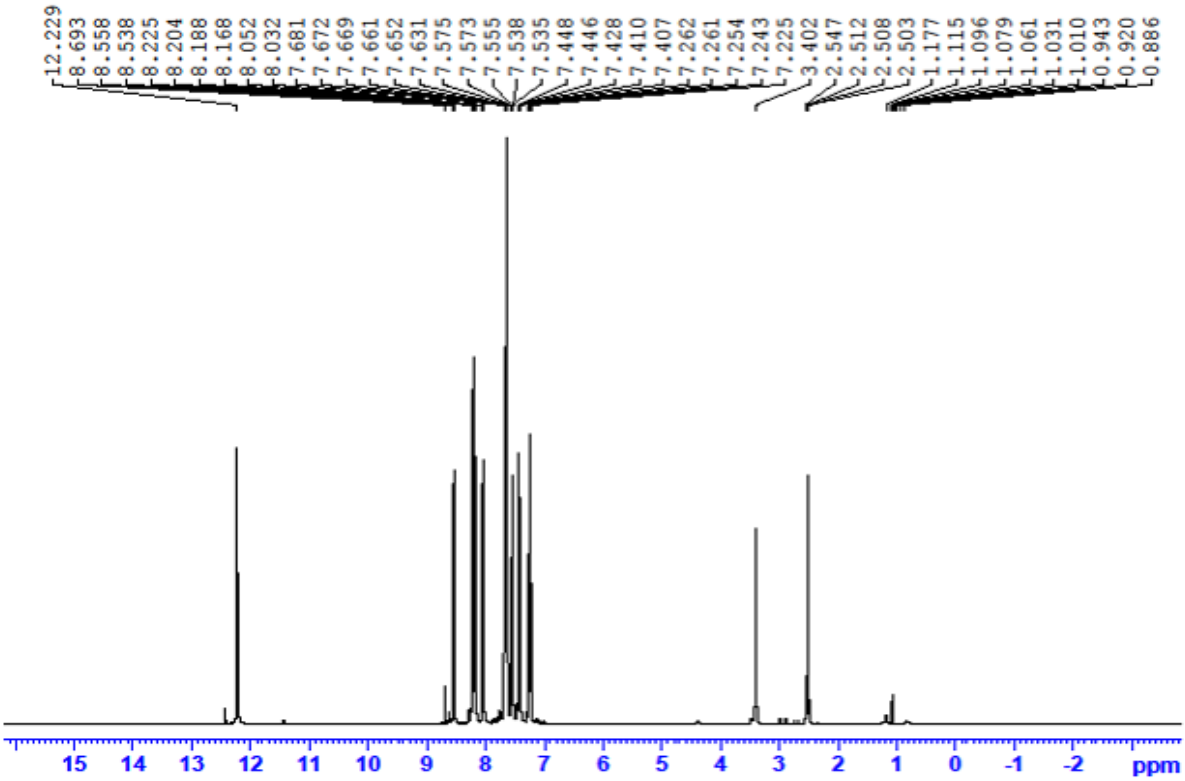


Figure 10. ^{1}H NMR Spectrum of 5-bromoacetyl -5,6-dihydro-11H-benzo[α]carbazole.

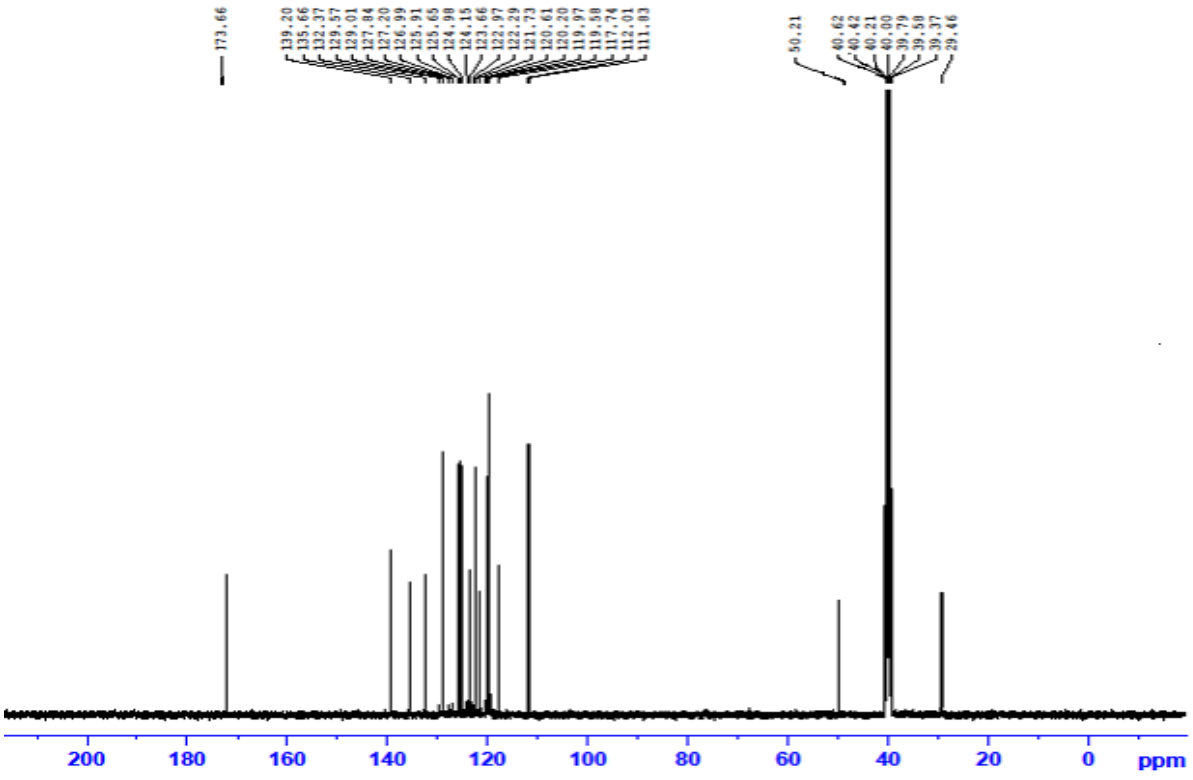


Figure 11. ^{13}C NMR Spectrum of 5-bromoacetyl -5,6-dihydro-11H-benzo[α]carbazole.

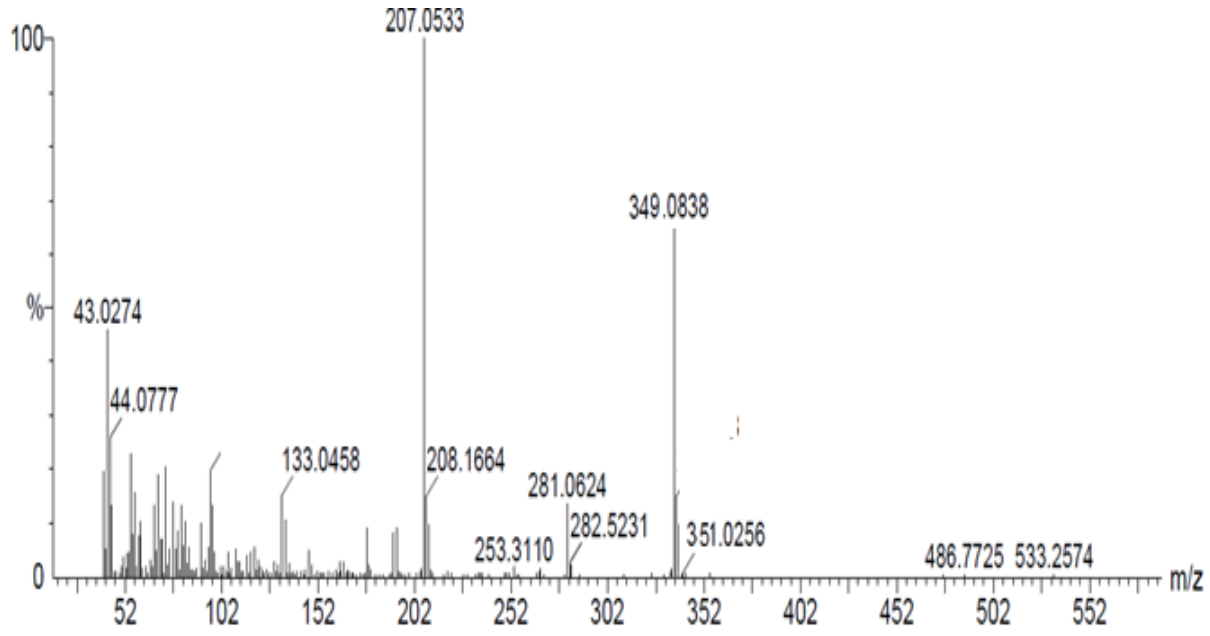


Figure 12. GC Mass Spectrum of 5-bromoacetyl -5,6-dihydro-11H-benzo[α]carbazole.

Figure 13. Antibacterial activity of synthesized compounds (zone of inhibhition)

ANTIBACTERIAL ACTIVITY

The results of antibacterial activity of synthesized compounds **A, B & C was** shown in table **1**. The zone of inhibition was indicated the nature of antibacterial activity. The synthesized compounds were subjected to *staphylococcus aureus, Bacillus species and Escherichia coli.* All the synthesized compounds **A, B & C,** found to have good antibacterial activity expressed in **Table 1**. The zone of inhibition pictures has shown in **Fig 13**.

TABLE 1.

Compound	ZONE OF INHIBITION						
	Control (DMSO)	*Staphylococcus Aureus*		*Bacillus*		*Escherichia Coli*	
	mm	mm	%	mm	%	mm	%
Ciprofloxacin	-	28	100	20	100	25	100
1	-	20	70	5	18	7	23.3
2	-	22	78.6	6	20	15	34.9
3	-	20	70	7	23	10	29

CONCLUSION

The bromoacetyl derivative of carbazole **A, B & C** were synthesized by enhanced approach with bromoacetylbromide in dimethylformamide. The synthesized compounds have been identified and confirmed using *Viz,* FTIR, 1H NMR, 13C NMR, Mass Spectral analysis.

The synthesized carbazole derivatives originate to have admirable antibacterial activity.

CONFLICT OF INTEREST

Authors do not have any conflict of interest.

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