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Novel Indole Derivatives with Improved Antimicrobial Activity

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ABSTRACT: *Heterocyclic compounds play a significant responsibility in the metabolism of living cell. Many of the heterocyclic compounds have pharmacological action and quantifiable uses. The chemistry of heterocyclic compounds had been an interesting field of study of long time. Chiefly, nitrogen containing heterocyclic compounds have customary special consideration in pharmaceutical chemistry due to their miscellaneous medicinal prospectives. Two set of compounds A and B have been synthesized in excellent yield through Fischer's indolosation method via acetic acid as a solvent. The synthesized compounds were characterized and established by various instrumental techniques viz, FTIR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy. The synthesized compounds were subjected to antimicrobial action. The outcome showed that the synthesized compounds exhibit brilliant antifungal activity than antibacterial activity.*
Keywords*: 2-pyrrolidinone, phenylhydrazine, acetic acid, ciprofloxacin, amphotericin-B*

I. INTRODUCTION

Indole derivatives have been a topic of substantial research interest and continue to be one of the most active areas of heterocyclic chemistry particularly due to their natural occurrence and pharmacological activities.[1]A large number of indole derivatives are at the fore of pharmacologically active lead compounds for drug development. Indole derivatives also occur widely in many natural product such as those from plants,[2] fungi[3] and marine organisms[4]. The isolation biological evaluation and chemical properties of natural product have attracted the attention of organic chemists, medicinal chemists, biologists and pharmacists chemical and biological research has also presented a great challenge to synthesis and optimize highly efficient and economical synthetic routes novel biologically activity substance.

At present there are approximately 1500 indole alkaloids describes [5]which includes simple and more complexly functionalized indole derivatives. The simple indole derivatives are comprised of a pyrrole ring fused with a benzene ring such as in the essential aminoacid.The medicinal use of the simple tryptamine alkaloids are relatively few serotonin 1 is one of the neurotransmitters in animals. Many indole derivatives found in plants have been noted to have hallucinogenic activity in humans, for example butotenine 2 and 5-methyl-N-methyl tryptamine.

Some simple indole alkaloids derivatives have also been isolated from marine sources. For example, methyl-(E)-3-(6-bromo-3-indolyl)-3-propenoate 3, a known sponge metabolite has been isolated from a number of sponges.[6-8]Due to their interesting biological activity induce the researches to synthesis carbazole. Carbazole have been found to possess a wide spectrum of biological activity such as antibacterial [9], antirheeumatoid arthritis [10], antitubercular [11], antiviral [12], antiepileptic [13], anti-inflammatory [14], and anti-cancer [15] activities. Also carbazole are a large and interesting group of organic compounds active among which one can find dyes stuffs [16] , and plastics [17], carbazole constitute an important class of naturally occurring heterocycles with interesting biological activities including their special affinity towards DNA. [18]

II. EXRERIMENTAL

2.1 Materials

N-methyl pyrrolidinone, 2-pyrrolidinone, phenylhydrazine and Chloroform were purchased from Avra synthesis Pvt.Ltd. The following chemicals were purchased from Avra synthesis Pvt.Ltd, Glacial aceticacid, Methanol.

2.2 Instruments

The Melting points of synthesized compounds were determined by open capillary tubes using an X-5A Melting point instrument and were uncorrected.IR Spectra were recorded on a Alpha Bruker FTIR Spectrometer using KBr pellets. The ^{1}H NMR Spectra were measured on a Bruker proton NMR-Avance 300MHz with chemical shift expressed in ppm downfield from TMS as internal standard in DMSO(d^{6}). The

^{13}C NMR Spectra were determined at 300MHz with a BrukerAvance Spectrometer. Mass Spectra were recorded on GC-MASS Spectrometer using methanol as a solvent.

2.3 Synthesis of 1,2,3,8 -tetra hydro-1-methyl pyrrolo(2,3- b) indole(A)

A mixture of n-methyl 2-pyrrolidinone(2.1ml)and glacial acetic acid (10ml) were taken in a round bottom flask fitted with reflux condenser phenyl hydrazine(1.7ml)was added slowly through the top of the condenser with constant stirring the reaction mixture was refluxed for 1.5 hours ,the disappearance of oily layer indicated the completion of the reaction and the hot mixture was poured in watch glass, the mixture was dried at room temperate. The crude product was crystallized out. Yield :85% ,Melting point 156-158℃, FTIR(KBr):3259cm^{-1}(N-H), 3024cm^{-1}(C-H aromatic), 2956-2858cm^{-1}(C-H aliphatic) , 1666cm^{-1} (C=C). ^{1}H NMR(DMSO d^{6}, ppm) : 9.9(s,N-H), 7.1 (m, 4H), 3.2-3.3 (t,2H), 2.7 (t,2H) & 2.5(s, 3H).^{13}C NMR (DMSO d^{6}): 136, 122, 119, 111 , 56, 38 & 21. Mass spectrum :M/Z ratio 172.1

2.4 Synthesis of 1,2,3,8- tetra hydro pyrrolo- 2,3 (b) indole(B)

A mixture of 2-pyrrolidinone (1.43ml) and glacial acetic acid (10ml) were taken in a round bottom flask fitted with reflux condenser phenyl hydrazine(1.87ml) was added slowly through the top of the condenser with constant stirring the reaction mixture was refluxed for about 3 hours, the disappearance of oily layer indicated the completion of the reaction and the hot mixture was poured in watch glass, the mixture was dried at room temperature. The crude product was scratched from watch glass and recrystallized from ethanol.

Yield :90% ,Melting point 135-137℃, FTIR(KBr):3246cm^{-1}(N-H), 3022cm^{-1}(C-H aromatic), 2937-2858cm^{-1}(C-H aliphatic) , 1655cm^{-1} (C=C). ^{1}H NMR(DMSO d^{6}), ppm) : 9.6, 8.9(2s,2N-H), 6.6-8.0 (m, 4H), 2.51-2.78 (d,2H) & 1.94-1.95 (d,2H). ^{13}C NMR (DMSO d^{6}): 149, 128, 118, 112,29 & 20. Mass spectrum :M/Z ratio 158.2.

2.5 Antimicrobial Activity

The antimicrobial activity of synthesized compounds against Escherichia coli, Bacillus subtilis and staphylococcus epidermidis, and fungi Candida albicans, Aspergillus flavus and Aspergillus niger were measured. Antimicrobial 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. Amphotericin B was used as reference antifungal agent and the method were called disc diffusion or Agar diffusion method.

III. RESULTS AND DISCUSSION

Synthesis of the desired 1,2,3,8 tetrahydro 1-methyl pyrrolo 23(b) indole have shown in scheme-1 by Fischer's Synthesis. The FTIR spectrum of the compound A have shown in Figure 1. The sharp intensity band at 3259cm^{-1} was observed due to the N-H stretching vibration. The medium band at 3024cm^{-1} was assigned to the aromatic =C-H stretching vibration. The sharp band appeared at 2858cm^{-1} and 2956cm^{-1}-2858cm^{-1} were associated with the aliphatic C-H Stretching vibration. The peak at 1666cm^{-1} was associated to the C=C stretching vibration. The peak appeared at 1373cm^{-1} was assigned to the C-N stretching vibration. Similarly, the peak at 1238cm^{-1} was observed for C-C stretching vibration.

The ^{1}H NMR spectrum of 1,2,3,8 Tetra hydro 1-methylpyrrolo 2,3-(b)indole have shown in Figure-2 .A singlet at 9.93ppm was due to N-H proton. The two doublet appeared at 7.03ppm and 7.18ppm corresponds to **a** protons. The triplet signal appeared at 3.287ppm and 3.321ppm equivalent to two protons represented by **b** protons. The triplets signal appeared at 2.708ppm corresponds to **c** proton. The value at 2.515ppm denotes as three proton singlet represented by **d** protons.

The compound A was also confirmed by using ^{13}C NMR shown in Figure 3. The peak appeared at 136,123ppm corresponds to the carbons neighbor to N-H. Aromatic carbons appeared at 111-122ppm and aliphatic carbons corresponds to the chemical shift value 21, 38 & 56. The mass spectrum of the compound was assigned to the molecular ion peak at m/z 172.1 which have shown in Figure 4.

Synthesis of the desired 1,2,3, 8- tetrahydropyrrolo 2,3 [b] indole have shown in scheme-2 by Fischer indole synthesis. The FTIR spectrum of the compound B shown in Figure 5. The sharp intensity band 3246cm^{-1} was observed due to the N-H stretching vibration. The medium band at 3022cm^{-1} was assigned to the aromatic =C-H stretching vibration. The sharp band appeared at 2937cm^{-1} and 2858cm^{-1} was associated with the aliphatic C-H stretching vibration. The peak at 1633cm^{-1} was associated to C=C stretching vibration. The peak appeared at 1733cm^{-1} and 1303cm^{-1} were assigned to the C-N stretching vibration and the peak at 1236cm^{-1} was observed due to C-C stretching vibration.

The ^{1}HNMR spectrum of 1,2,3,8- tetra hydro pyrrolo 2,3(B) Indole have shown in Figure 6. A singlet at 9.640ppm was represented to N-H proton. The two singlet appeared at 8.074ppm and 7.638ppm corresponds to **a** proton. The triplet signal at 7.122ppm and 6.770ppm corresponds to two equivalent protons represented by **b** protons. The two doublets for 2.788ppm and 2.518ppm was due to **c** proton The two doublet signal at 1.95ppm and 1.92ppm corresponds to **d** protons

The compound B was also confirmed by using ^{13}C NMR spectrum shown in Figure 7. The peak appeared at 149ppm and 128ppm corresponds to the carbon atom present near to nitrogen atom. The signal at 118ppm, 112ppm & 111ppm corresponds to aromatic carbons. The aliphatic carbons showed the signals at 29ppm & 20ppm. The mass spectrum of the compound was assigned to the molecular ion peak at m/z 158.2 have shown in Figure 8.

The synthesized compounds were subjected to antimicrobial activity against three bacteria Escherichia coli, Bacillus subtilis and staphylococcus epidermidis, and fungi Candida albicans, Aspergillus flavus and Aspergillus niger respectively. Compound B shows good antibacterial activity and compound A shows moderate activity. The synthesized two compounds show excellent antifungal activity against Aspergillus flavus and Aspergillus niger.

IV. CONCLUSIONS

Carbazole derivatives have been synthesized by simple Fischer indole synthesis with suitable solvent. The synthesized compounds were confirmed by various spectral techniques viz., FTIR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy. The synthesized compounds found to have excellent antifungal activity than antibacterial activity. Among the synthesized compounds A & B, compound B posses good antibacterial activity due its two functional N-H group.

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Spectral analysis

Table. 1 Antibacterial activity

Compound	ZONE OF INHIBITION					
	Escherichia coli		Bacillus subtilis		Staphylococcus epidermidis	
	Mm	%	Mm	%	mm	%
Ciprofloxacin	28	100	20	100	20	100
A	8	28.5	-	-	8	40
B	15	53.5	7	35	8	40

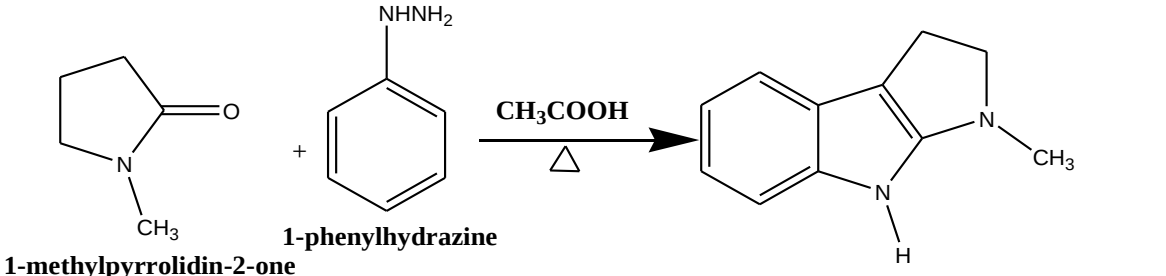
Table.2 Antifungal activity

Compound	ZONE OF INHIBITION					
	Candida albicans		Aspergillus flavus		Aspergillus niger	
	mm	%	mm	%	mm	%

Amphotericin-B	15	100	30	100	28	100
A	-	-	60	200	36	128.5
B	-	-	50	66.6	50	178.5

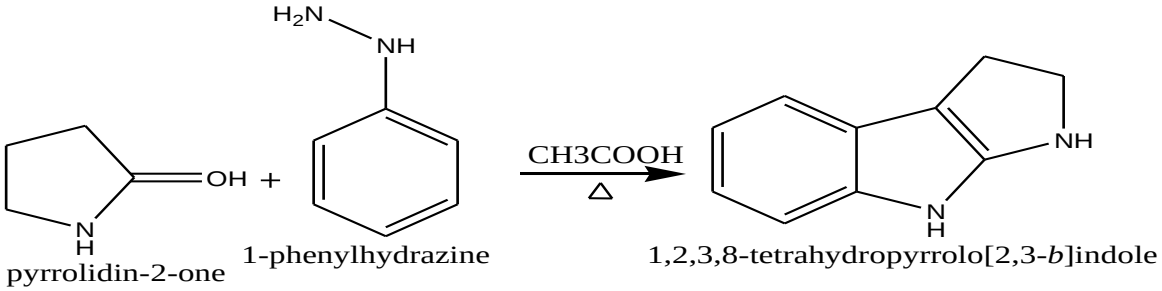
Reaction Scheme-Fischer,S Synthesis

SCHEME-1



1-methylpyrrolidin-2-one **1-phenylhydrazine** **1,2,3,8-tetrahydro-1-methylpyrrolo[2,3-*b*]indole**

SCHEME-2



pyrrolidin-2-one 1-phenylhydrazine 1,2,3,8-tetrahydropyrrolo[2,3-*b*]indole

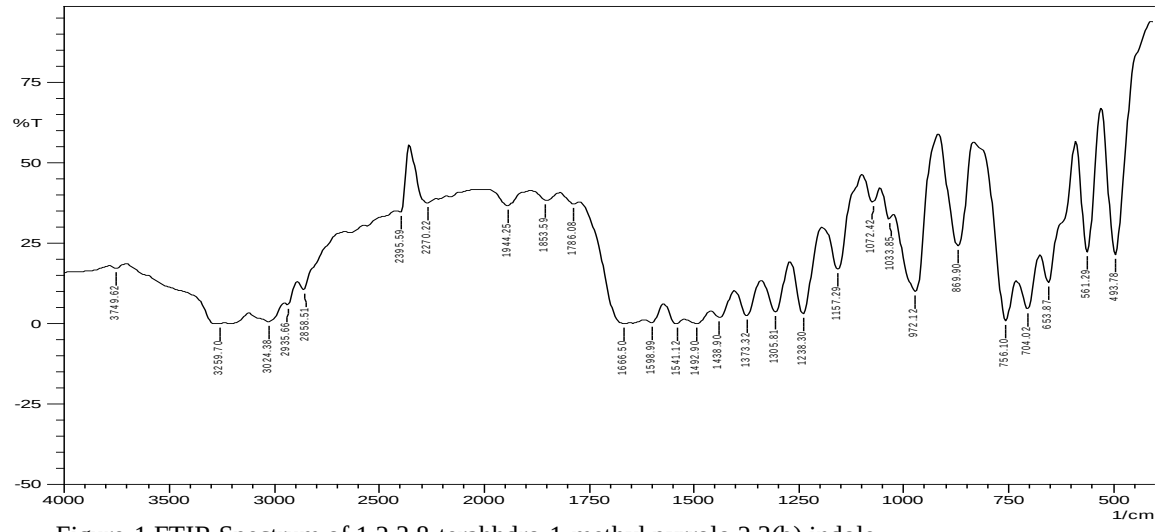


Figure-1 FTIR Spectrum of 1,2,3,8-terahhdro-1-methyl pyrrolo 2,3(b) indole.

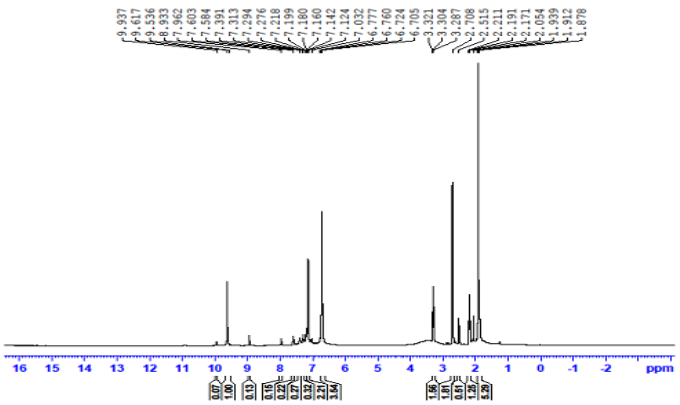


Figure-2 [1]H Spectrum of 1,2,3,8-terahhdro-1-methyl pyrrolo 2,3(b) indole.

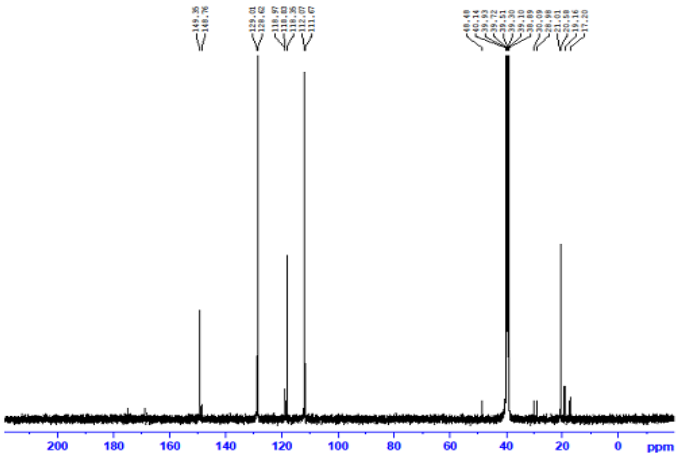


Figure-3 [13]C Spectrum of 1,2,3,8-terahhdro-1-methyl pyrrolo 2,3(b) indole.

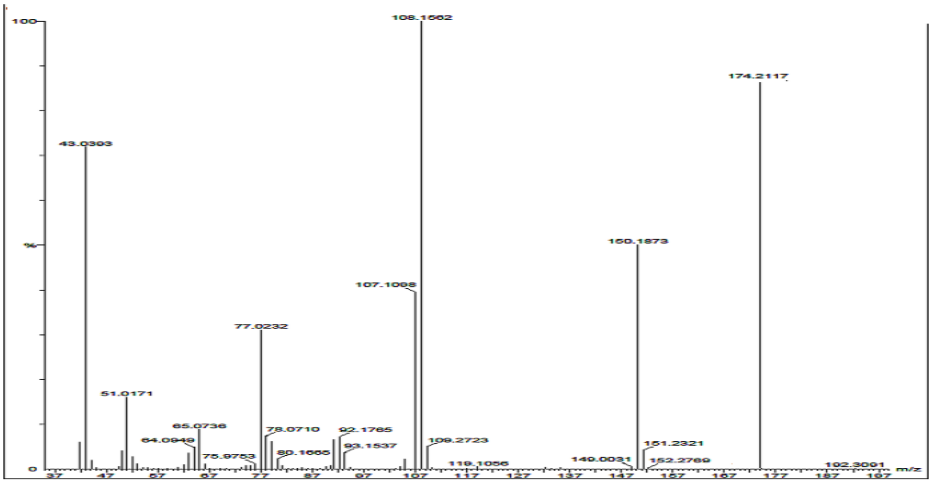


Figure-4 GC MASS Spectrum of 1,2,3,8-terahhdro-1-methyl pyrrolo 2,3(b) indole.

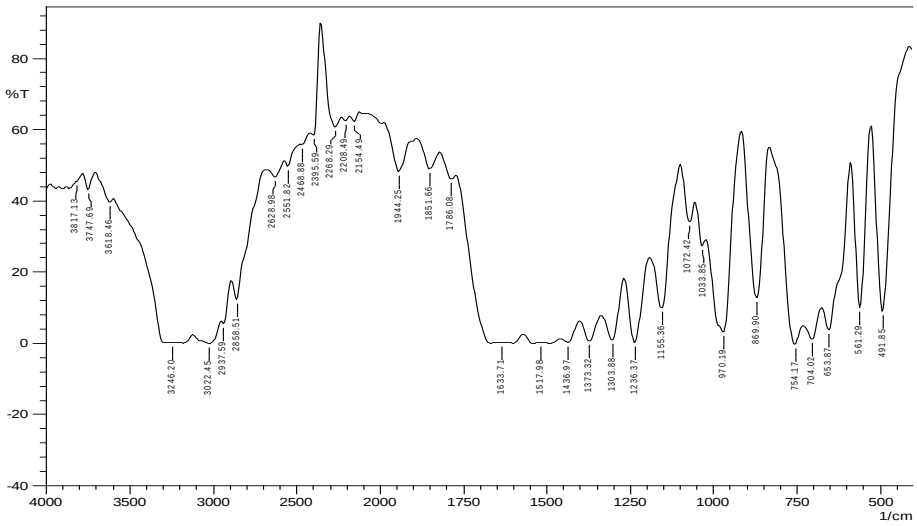


Figure-5 FTIR Spectrum of 1,2,3,8-terahhdro pyrrolo 2,3(b) indole.

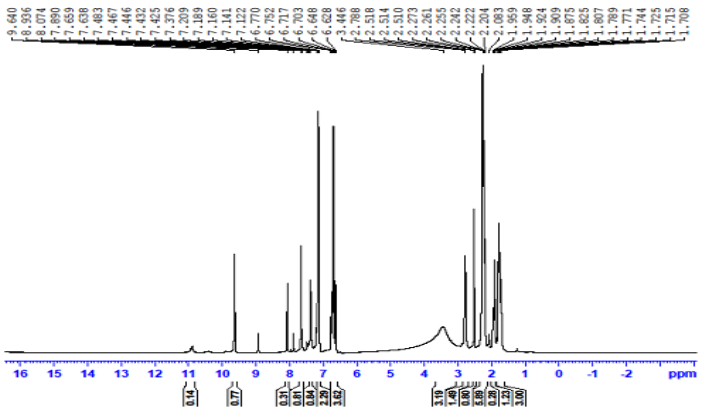


Figure-6 ^{1}H Spectrum of 1,2,3,8-terahhdro pyrrolo 2,3(b) indole.

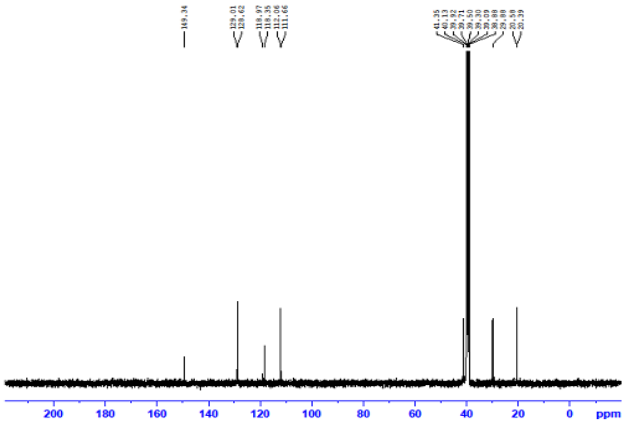


Figure-7 ^{13}C Spectrum of 1,2,3,8-terahhdro pyrrolo 2,3(b) indole.

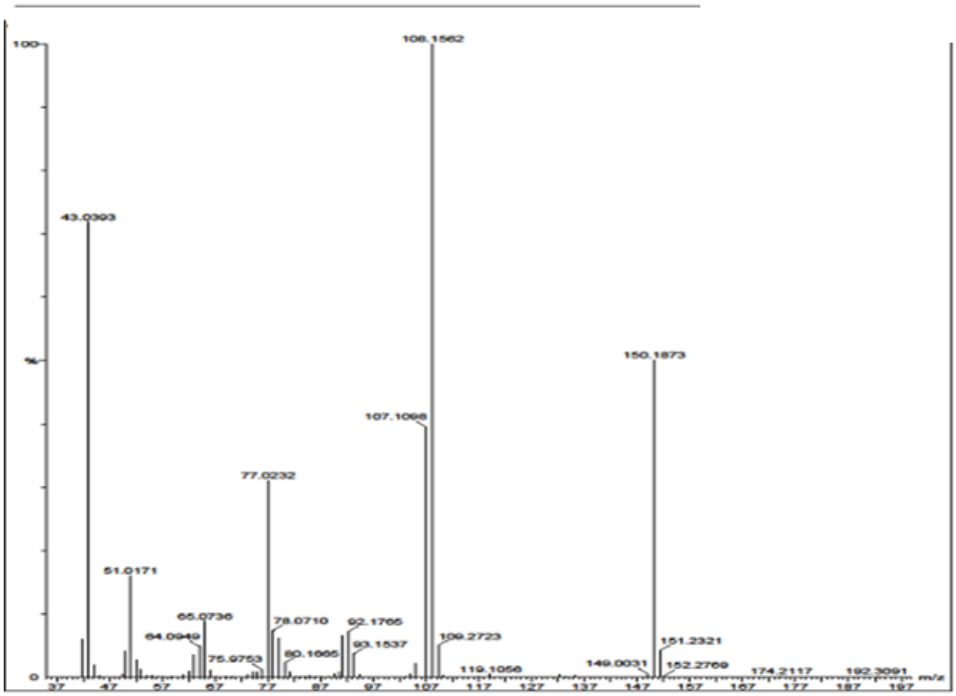
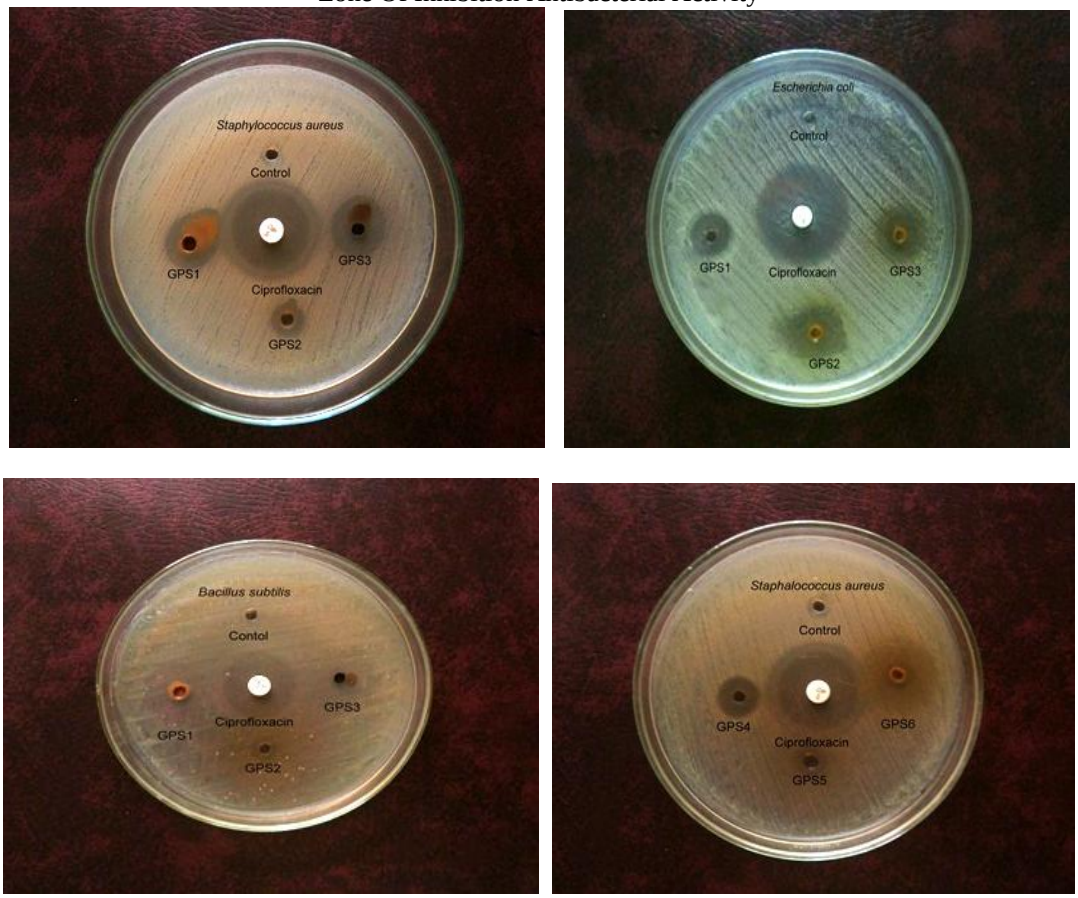
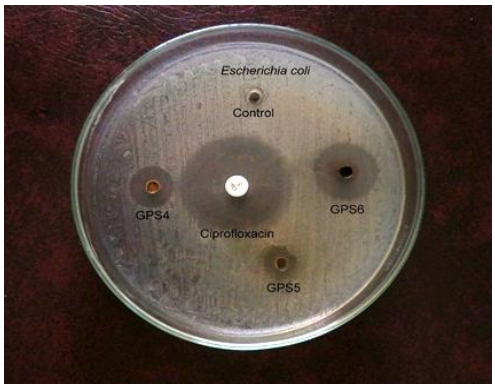
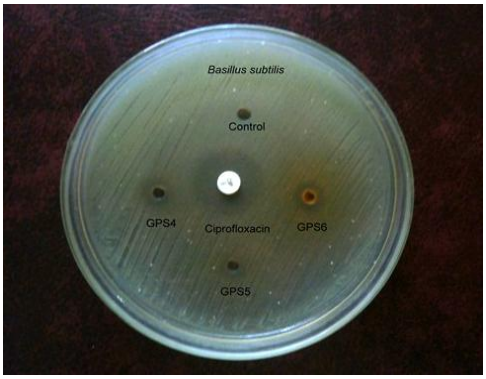


Figure-8 GC MASS Spectrum of 1,2,3,8-terahhdro pyrrolo 2,3(b) indole.

Zone Of Inhibition Antibacterial Activity







Antifungal Activity