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ELECTROPHILIC AND FREE RADICAL BROMINATION OF NOVEL [b] CARBAZOLE DERIVATIVES AND ANTIMICROBIAL EVALUATION

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ABSTRACT
Heterocyclic compounds containing N,O & S moieties comprise of Potentially active compounds against bacteria and fungi. The synthesis of substituted and condensed indole has been attracted due to their importance in biological activity. Synthesized compounds by an improved approach using Fischer's synthesis have been designated as 1,2,3,4-tetrahydrocyclopenta(b)indole followed by an electrophilic and free radical bromination using N-bromo succinimide. The formation of all compounds were confirmed by spectral techniques *Viz*, FTIR, ^{1}H NMR, ^{13}C NMR, MASS Spectroscopy. The compounds have also been suggested for antimicrobial action.

KEYWORDS: Heterocyclic compounds, Sulphuric acid, Phenylhydrazine, Ciprofloxacin, Amphotericin-B.

INTRODUCTION
Heterocyclic compounds are widely distributed in nature and occupy a prominent place in medicinal chemistry as pharmaceuticals and drug intermediates (Brown, 1984; petrie et al, 1985). Heterocyclic compounds containing nitrogen, sulphur and oxygen moieties constitute the core structure of a number of biologically interested compounds, against bacteria and fungi.[1,2] Nitrogen containing heterocyclic such as indole or carbazole are probably the most widely spread nitrogen heterocycles in nature.[3] A survey of the pertinent literature revealed that carbazole have been found to possess a wide spectrum of biological activity such as antibacterial,[4] antirheaumatoid arthritis,[5] antitubercular,[6] antiviral,[7] antiepileptic,[8] anti-inflammatory,[9] and anti-cancer.[10-11] activities. Also, carbazole is a large and interesting group of organic compounds active, among which one can find dyes stuffs,[12] and plastics,[13] carbazole constitute an important class of naturally occurring heterocycles with interesting biological activities including their special affinity towards DNA.[14]

Mono-aryl hydrazines 5 are important intermediates in the synthesis of a number of heterocycles, including indoles,[15] and few azoles, which exhibit biological activity and are used in drug development.[16] Aryl hydrazines 6 are also the key intermediates in the preparation of stable radicals such as Verdazy,[17] and benzo,[15,16,18] triazinyls,[19] Recently Knolker and Reddy extensively reviewed the synthesis of biologically active carbazole alkaloids.[20] In spite of reporting various methods for the synthesis of indoles,[21] Fischer indole synthesis is probably the most widely investigated synthesis of indole and carbazole derivatives.

The Fischer indole is a chemical reaction that produces an aromatic heterocyclic indole from a (substituted) phenylhydrazine and an aldehyde or ketone under acidic conditions. The reaction was discovered in 1883 by Hermann Emil Fischer.[22] Today the antimigraine drugs of the tryptophan class is often synthesized by this method. The choice of acid catalyst is very important, Bronsted acids such as HCl, H_2SO_4, polyphosphoric acid and p- toluenesulfonic acid have been used successfully, while Lewis acids such as boron trifluoride, zinc chloride, iron chloride and aluminium chloride are also useful catalyst.[23-24]

The tricyclic cyclopenta(b)indole ring system is a common structural element of a large varity of indole alkaloids.[25] More specifically, the cyclopenta(b)indole ring system occurs in a number of medicinally important tremorgenic mycotoxins (janthitrems, penitrems, paspaline etc),[26] and monoterpenoid alkaloids such as yeuhchukene,[27] Morever, cyclopenta(b)indole derivatives were reported to exhibit a strong biological activity and inhibit RNA polymerase,[28] modulate activity of liver -X-receptor which are agonists of the human 5-HT2c receptor.

The derivative of cyclopenta(b)indole are useful for the treatment and prevention of central nervous system disorders, including obsessive – compulsive disorder, depression, anxiety, generalized anxiety disorder,

schizophrenia, panic disorder, migraine, sleep disorders, such as sleep apnea, eating disorders, such as hyperphagia, obesity, epilepsy and spinal cord injury. (Welmaker et al. 2007)

Frφyen reported the halogenations of carboxylic acid using a combination of triphenylphosphine and N-bromosuccinimide.[29] Synthesis of dibromo heterocyclic compounds in presence N-bromo succinimide /H_2SO_4 have also been experienced as brominating agent according to the literature.[30] The reaction proceeds well in room temperature to give excellent yield. The scope of the work is to synthesis bromo derivatives carbazole followed by antimicrobial evaluation.

EXPERIMENTAL

MATERIALS AND METHODS

Cyclopentanone and Chloroform were purchased from Merk. Concentrated sulphuric acid, phenylhydrazine were purchased from Avra synthesis Pvt.Ltd. The Melting points of synthesized compounds were determined by open capillary tubes using an X-5A Melting point instrument and were uncorrected. FTIR 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 400 MHz with chemical shift expressed in ppm downfield from TMS as internal standard in DMSO (d_6). The ^{13}C NMR Spectra were determined at 400 MHz with a Bruker Avance Spectrometer. Mass Spectra were recorded on GC-MASS Spectrometer using methanol as a solvent.

Synthesis of 1,2,3,4-Tetra Hydrocyclopenta[b]Indole (1)

Concentrated Sulphuric acid (18M, 2.19ml) was added dropwise to a mixture of phenylhydrazine (10.2 mmol, 3.45g) and cyclopentanone (10.2 mmol, 2.4g) in water(15.65ml). The resulting mixture was heated to reflux for 30 minutes and then allowed to cool to room temperature. Hexane (15ml) was added to the flask and the mixture was heated to reflux. The yellow hexane solution was decanted hot from the mixture and placed in the freezer. More hexanes is added to the flask and the procedure repeated two more times using a total volume of 60ml of hexanes. After 1 hour in the freezer, the solid was collected from the flasks and dried. The dried product was recrystallized from ethyl acetate.

Yield :70%, Melting point 99-102℃, FTIR(KBr):3392cm^{-1}(N-H), 3041cm^{-1}(C-H aromatic), 2927cm^{-1} and 2856cm^{-1}(C-H aliphatic), 1450cm^{-1} (C=C), 1367cm^{-1} (C-N),1294 cm^{-1}(C-C). ^{1}H NMR ($CDCl_3$, ppm) :7.763(S, N-H),7.05-7.10(2d,2H),7.23-7.43(2dd,2H), 2.8-2.86 (2t,4H),2.5-2.56(m,2H). ^{13}C NMR (DMSO d^6):144,140,111-124,28,25 & 24. Mass spectrum: m/e ratio 157.3.

Synthesis of 2, 7-Dibromo 1,2,3,4-Tetra Hydro Cyclo Penta[b] Indole (2)

N- bromosuccinimide (NBS) (10.82 g, 0.06 mol) was slowly added to a solution of 1,2,3,4-tetrahydrocyclopenta [b] indole (5.2g, 0.03 mol) in 85% sulphuric acid and the mixture was vigorously stirred overnight at room temperature. This mixture was poured into ice cold water taken in a beaker, and stirred well. The 2,7-dibromo 1,2,3,4-tetra hydrocyclopenta (b) indole was purified using hot ethanol and further purification by recrystallization from ethyl acetate afforded a dark maroon powder.

Yield :80%, Melting point 168-170℃, FTIR(KBr): (N-H Str) 3360cm^{-1},(=C-H Str) 3238cm^{-1},(C-H Str) 2854-2922cm^{-1},(C=C Str) 1683cm^{-1},(C=C-Br Str),1456cm^{-1},(C-C Str) 1219cm^{-1},(C-N Str)1039cm^{-1},(C-Br Str) 869cm^{-1}. ^{1}H NMR (DMSO d_6): 8.22ppm (S,N-H), 8.16ppm(S,H), 7.48-7.51ppm (d,H), 7.80ppm (d,H),3.40-3.45ppm (H,m), 2.88-2.89ppm (d,2H), 2.98-2.99ppm (d,2H). ^{13}C NMR(DMSO d_6):124, 128, 115-118, 56.03, 32.6 & 29.5. Mass spectrum: m/e ratio 315.

Synthesis of 6-Bromo-1,2,3,4-Tetra Hydrocyclopenta [b]INDOLE (3)

The synthesis of 6-bromo-1,2,3,4-tetrahydro cyclopenta [b]indole have shown in scheme 2. The scheme reveals that the mixture of 4-bromo phenylhydrazine hydrochloride (8.4mmol, 1.893g) and cyclopentanone (8.4mmol, 0.3563g) in 10ml of glacial acetic acid were taken in RB flask fitted with reflux condenser. The content was allowed to reflux for 1hour. After the completion of reaction, the content was poured in to crushed ice cold water with constant stirring. The crude solid was filtered off and washed with water then allowed to dried. The dried precipitate was recrystallised with hot methanol to obtain pure 6-bromo-1,2,3,4-tetrahydro cyclopenta[b]indole.

Yield:80%, Melting point 112-114 ℃, FTIR(KBr):3414cm^{-1}(N-H), 3059cm^{-1}(C-H aromatic), 2856cm^{-1}(C-H aliphatic) 1489cm^{-1} (C=C). ^{1}H NMR (DMSO d-6, ppm): 11.0 (S, N-H),7.05-7.25(2d,2H), 7.43(S,H), 2.4-2.8 (m,4H),2.2-2.4 (m,2H). ^{13}C NMR (DMSO d-6):113-146, 25, 28 & 29. Mass spectrum:m/e ratio 273.1(M+).

Synthesis of 2,6-Dibromo-1,2,3,4-Tetrahydrocyclopenta [B]Indole

6-bromo-1,2,3,4-tetrahydrocyclopenta[b]indole (0.7556g, 0.0032mole) was dissolved in 20ml of dichloromethane and N-bromosuccinimide (0.5696g, 0.0032mole) was added with 10mg of benzoyl peroxide has free radical initiator. The mixture was warmed up to 75°C and maintained at this temperature under room temperature. The crystals was filtered off, the solvent was evaporated to dryness and the solid residue was purified by column chromatography on silica gel, eluent: ethyl acetate: hexane, 1:9 v/v. By evaporating fractions

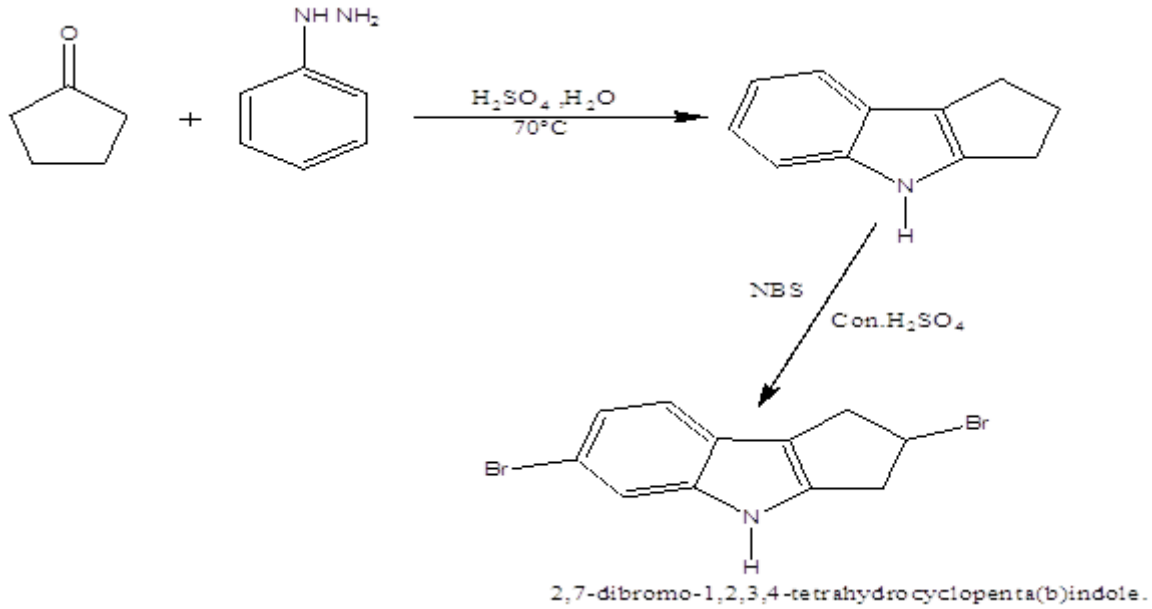
containing only expected product the pure compound was obtained.

Yield :90%, Melting point 148-150℃, FTIR(KBr): (N-H Str) 3406cm^{-1},(=C-H Str) 3082cm^{-1},(C-H Str) 2850cm^{-1},(C=C Str),(C-Br Str) 805cm^{-1}. ^{1}H NMR (DMSO d_6): 8.7ppm (S,N-H), 8.5ppm(S,H), 7.5-76ppm (d,H), 2.40-2.5ppm (H,m), 2.4-2.5ppm (d,2H). ^{13}C NMR(DMSO d_6): 111-133, 56.03, 29 & 20. Mass spectrum : m/e ratio 315.2.

Evaluation of Antimicrobial Activities

Agar Well Diffusion Method

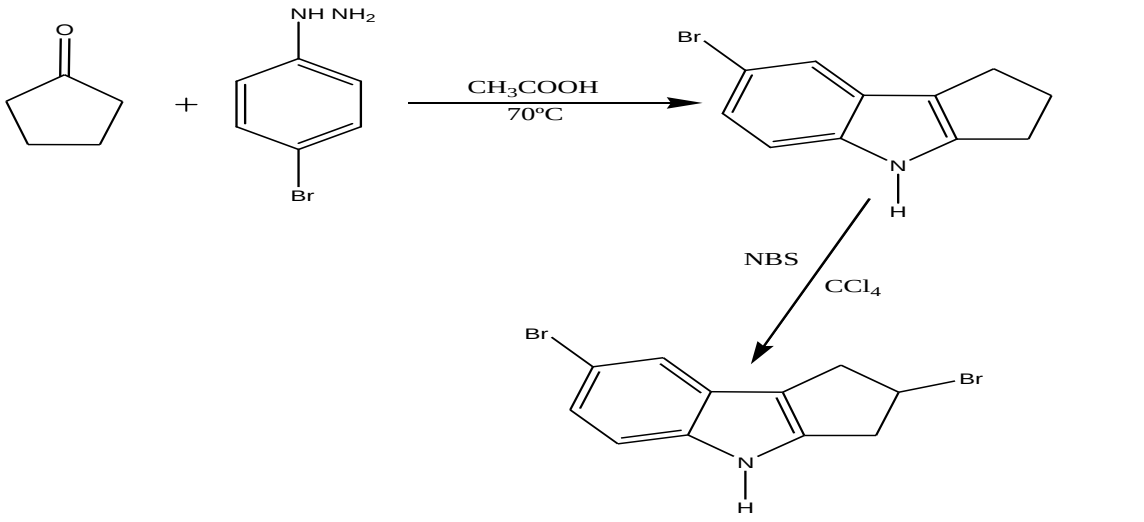
Antimicrobial analysis was followed using standard agar well diffusion method to study the antibacterial and antifungal activity of compounds. The test organisms were flood-inoculated onto the surface of BHI agar and then dried. Five-millimeter diameter wells were cut from the agar using a sterile cork-borer and 30 µL of the sample solution were poured into the wells. The plates were incubated for 18 h at 37°C for bacteria and at room temperature for fungi. 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. 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 measured.



2,7-dibromo-1,2,3,4-tetrahydrocyclopenta(b)indole.

Reaction Scheme **1** (Ref: New electron – accepting π-conjucated polyquinoxalines with fluorene unit: synthesis and light emitting properties.(S.H.Jung [1],D.H.Suh[2], H.N.Cho[1], 19 April 2003). Polymer Bulletin)

Reaction Scheme 2



2,6-dibromo-1,2,3,4-tetrahydrocyclopenta(b)indole.

RESULT AND DISCUSSION

1,2,3,4-Tetra Hydrocyclopenta[B]Indole (1)

The (b) carbazole derivatives were synthesised by Fischer indole synthesis of derivative of cyclopentanone with phenyl hydrazine. The FTIR spectrum (**Fig 1**) of the compound was denote the medium intensity band at 3392 cm^{-1} corresponds to the N-H stretching vibration. The sharp medium band at 3041 cm^{-1} was associated the aromatic C-H stretching vibration. The sharp band appeared at 2927 and 2856 were assigned to the aliphatic C-H stretching vibration. In the ^{1}NMR spectrum a singlet at 7.76δ was due to N-H proton. The two doublets at 7.05-7.10 δ the triplet signal at 7.23 δ - 7.43 δ equivalent to 2H aromatic protons. The 2.8-2.86 δ and two quintets centered at 2.5-2.56 δ value corresponds to aliphatic protons in **Fig 2**. ^{13}C NMR (DMSO d_6) The peak appeared at 140 ppm and 144 ppm corresponds to the carbon atoms present neighbouring to the nitrogen atom. The spectral value111-124ppm corresponds to aromatic carbons represented by **Fig 3**. The aliphatic carbon atoms had shown the spectral peak at 24 ppm, 25 ppm and 28 ppm. Mass spectrum:m/e ratio 157.3. (**Fig 4**)

Table 1: Antibacterial activity.

Compound	Zone of Inhibition					
	Pseudomonas aeruginosa		*Bacillus species*		*Staphylococcus epidermidis*	
	mm	%	mm	%	mm	%
Ciprofloxacin	20	100	22	100	30	100
2	-	-	12	54.5	14	46.6
4	7	35	13	59	15	50

TABLE 2: Antifungal activity

Compound	Zone of Inhibition					
	Candida tropicalis		*Aspergillus flavus*		*Aspergillus niger*	
	mm	%	mm	%	mm	%
Amphotericin-B	20	100	30	100	30	100
2	9	45	8	26.6	8	26.6
4	20	100	30	100	30	100

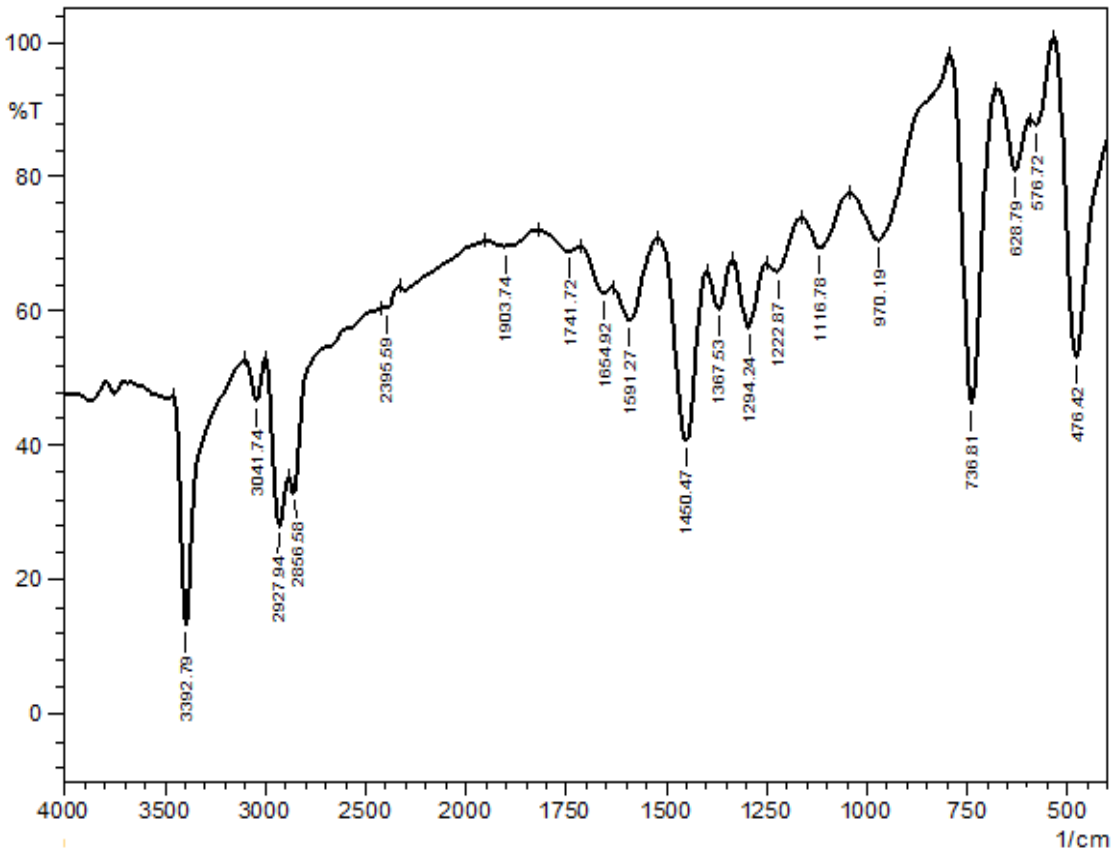


Figure 1: FTIR Spectrum of 1,2,3,4-tetrahydrocyclopenta[b]indole.

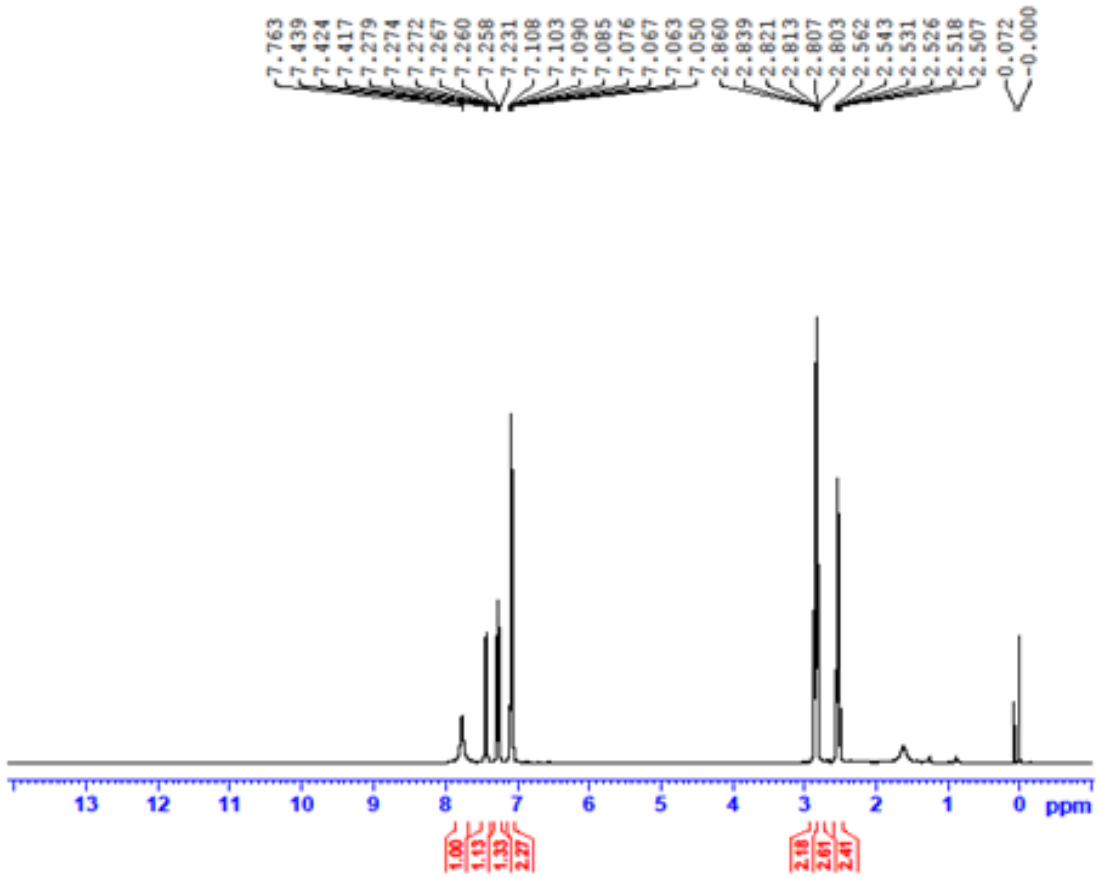


Figure 2: ^{1}H NMR Spectrum of 1,2,3,4-tetrahydrocyclopenta[b]indole.

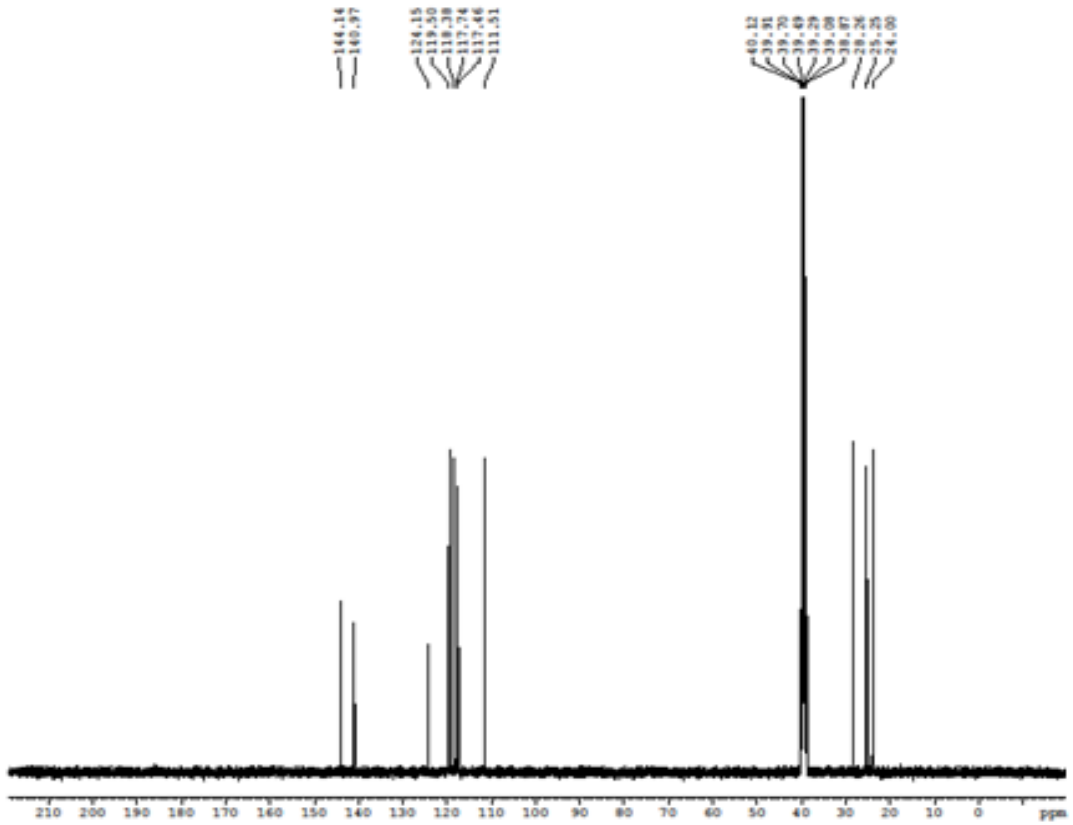


Figure 3: ^{13}C NMR Spectrum of 1,2,3,4-tetrahydrocyclopenta[b]indole.

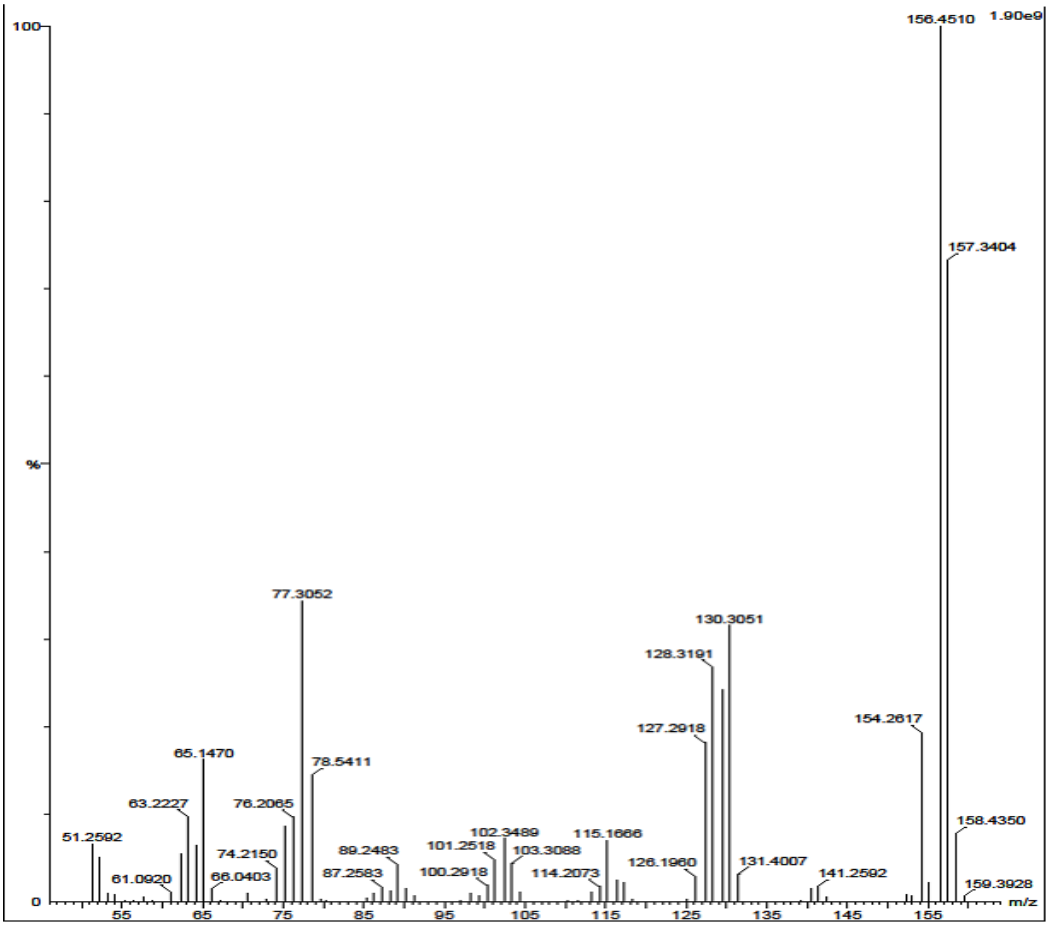


Figure 4: GC MASS Spectrum of 1,2,3,4-tetrahydrocyclopenta[b]indole.

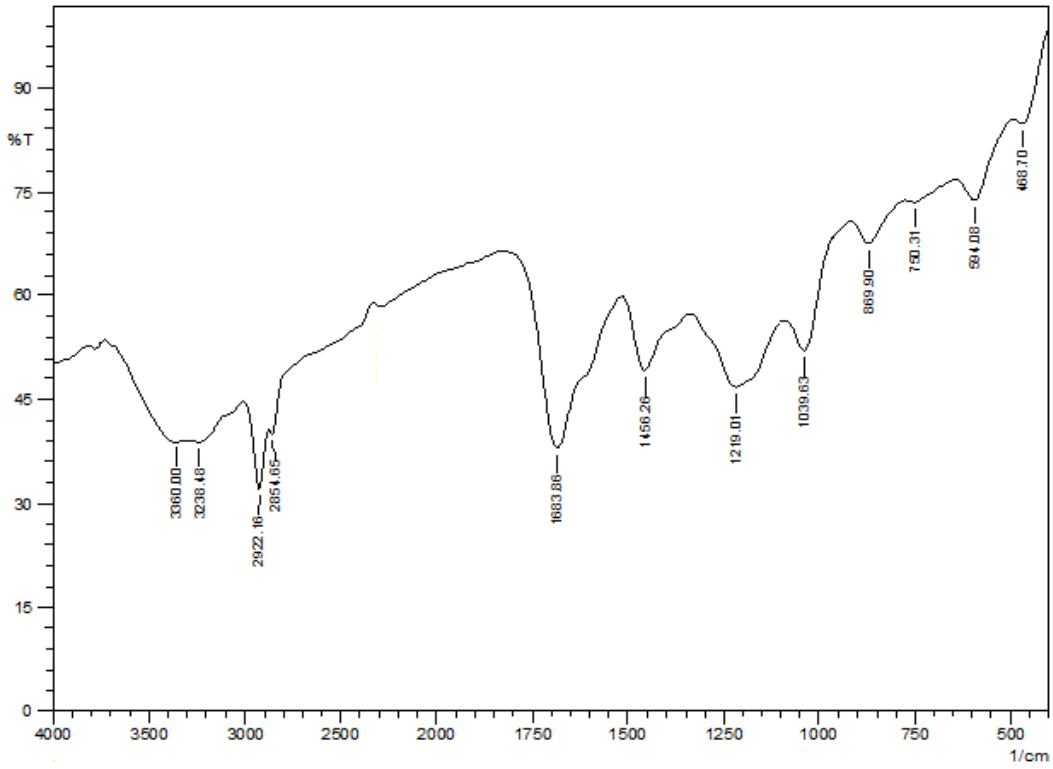


Figure 5: FTIR Spectrum of 2,7-dibromo-1,2,3,4-tetrahydrocyclopenta[b]indole.

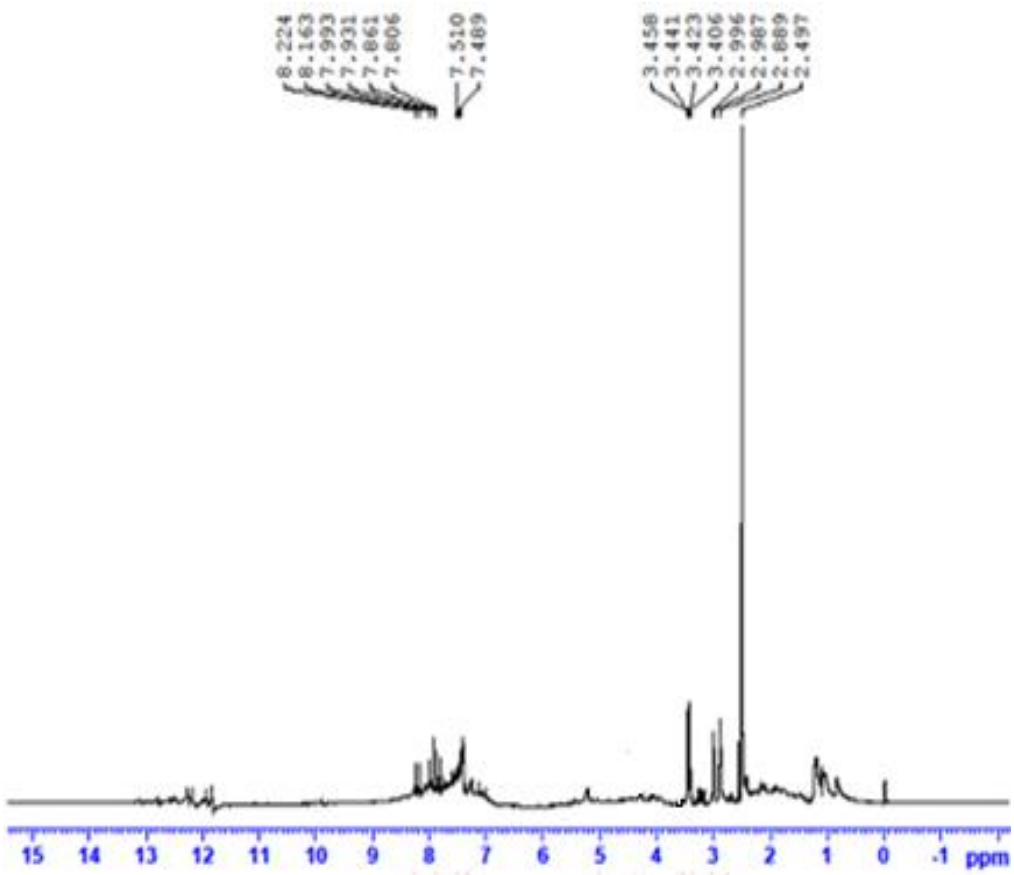


Figure 6: ^{1}H NMR Spectrum of 2,7-dibromo-1,2,3,4-tetrahydrocyclopenta[b]indole.

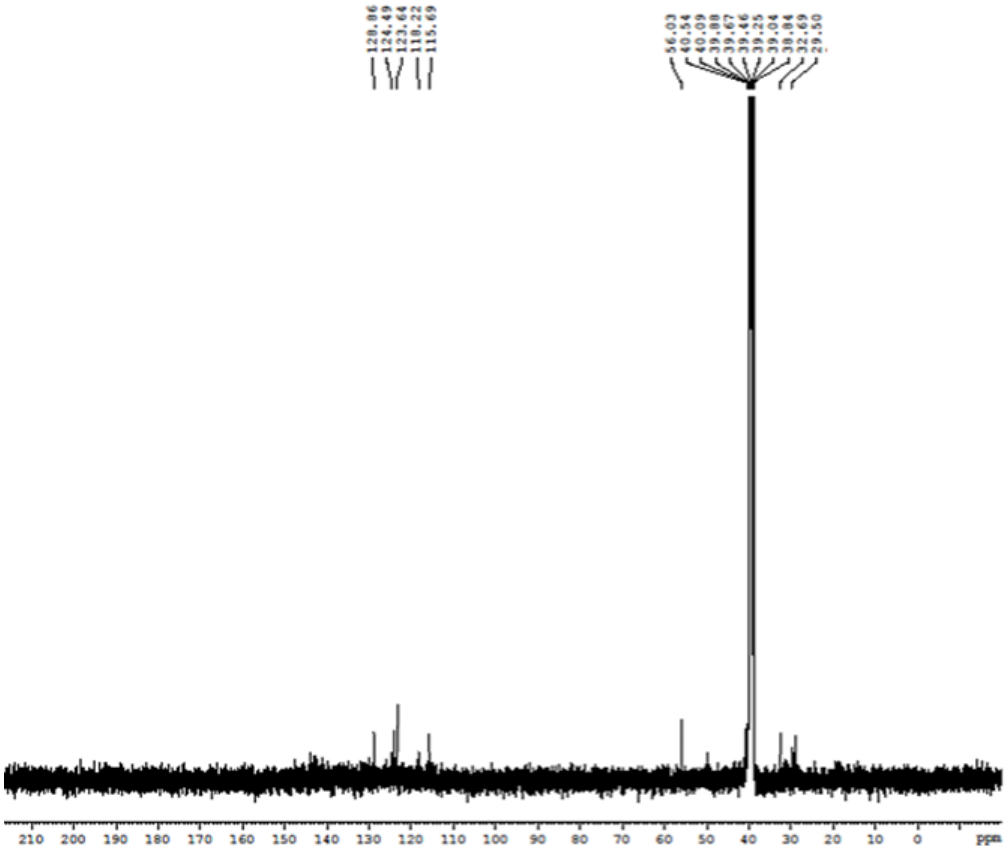


Figure 7: ^{13}C NMR Spectrum of 2,7-dibromo-1,2,3,4-tetrahydrocyclopenta[b]indole.

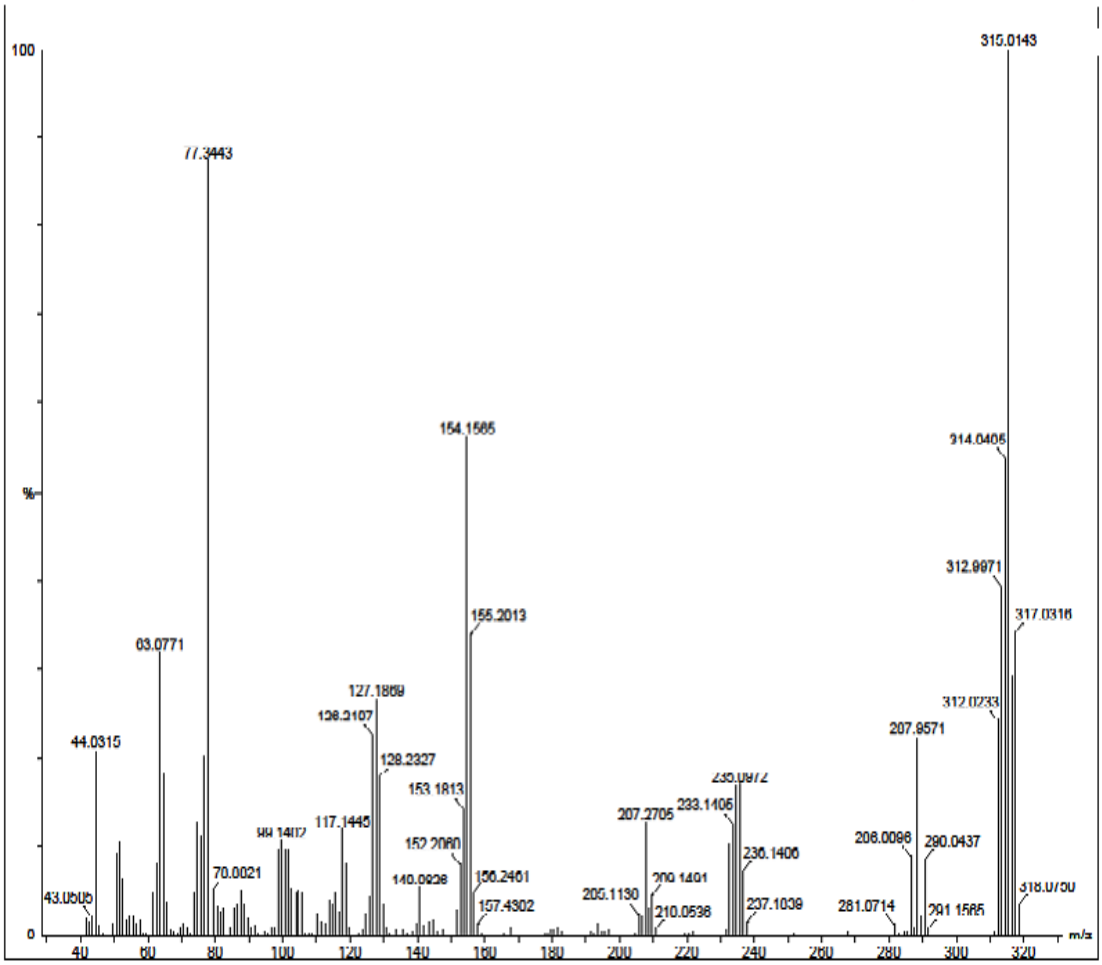


Figure 8: GC MASS Spectrum of 2,7-dibromo-1,2,3,4-tetrahydrocyclopenta[b]indole.

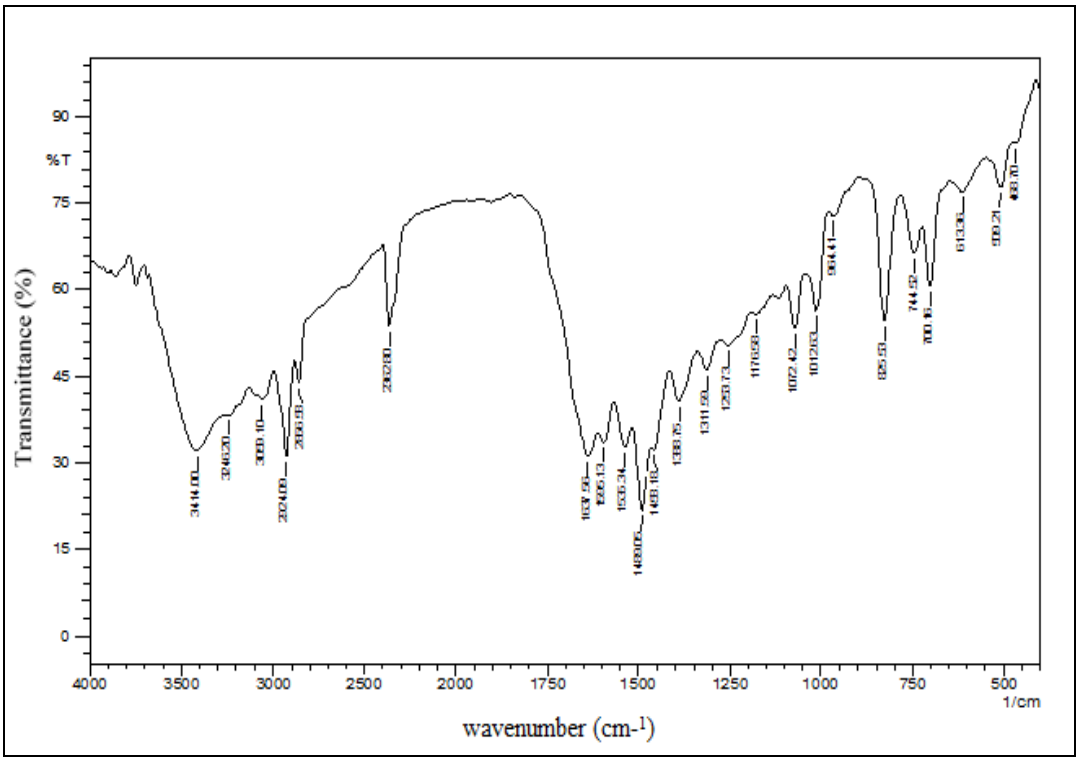


Figure 9: FTIR spectrum of 6-Bromo-1,2,3,4-tetrahydro cyclopenta[b]indole.

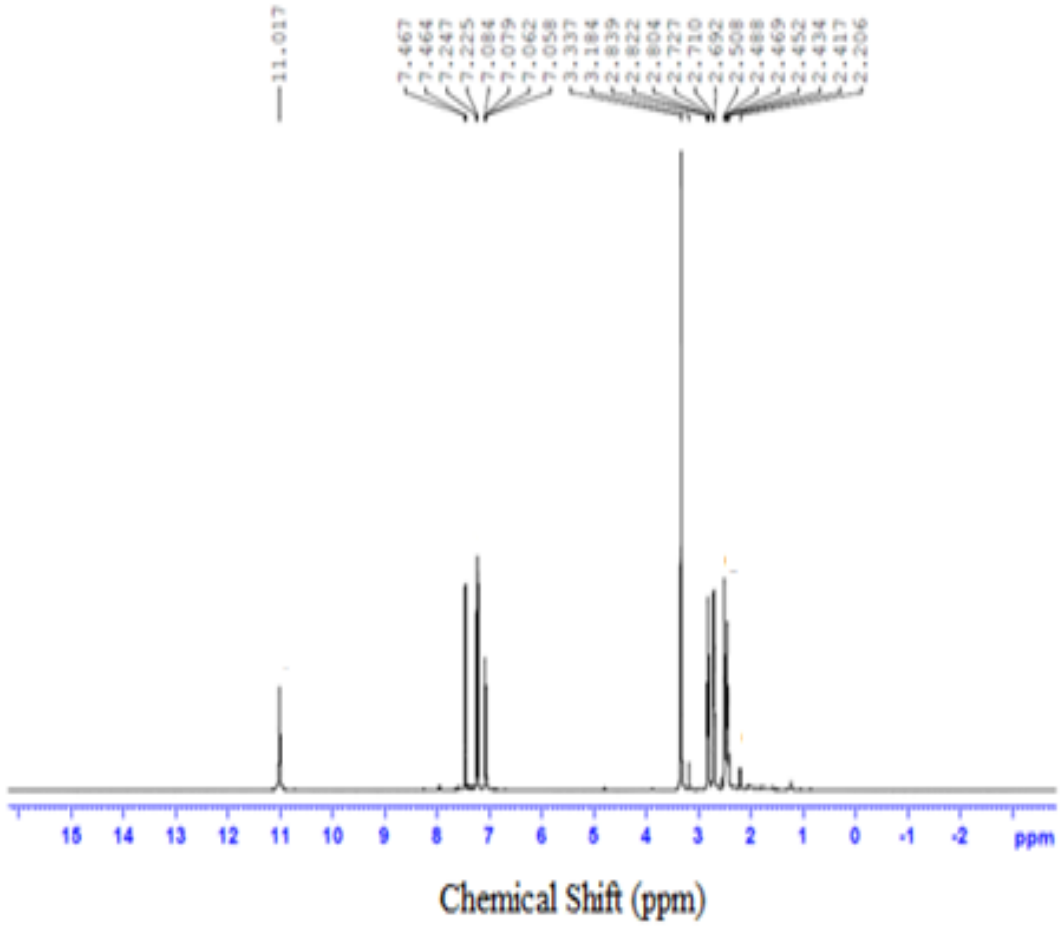


Figure 10: ^{1}H NMR spectrum of 6-Bromo-1,2,3,4-tetrahydro cyclopenta[b]indole.

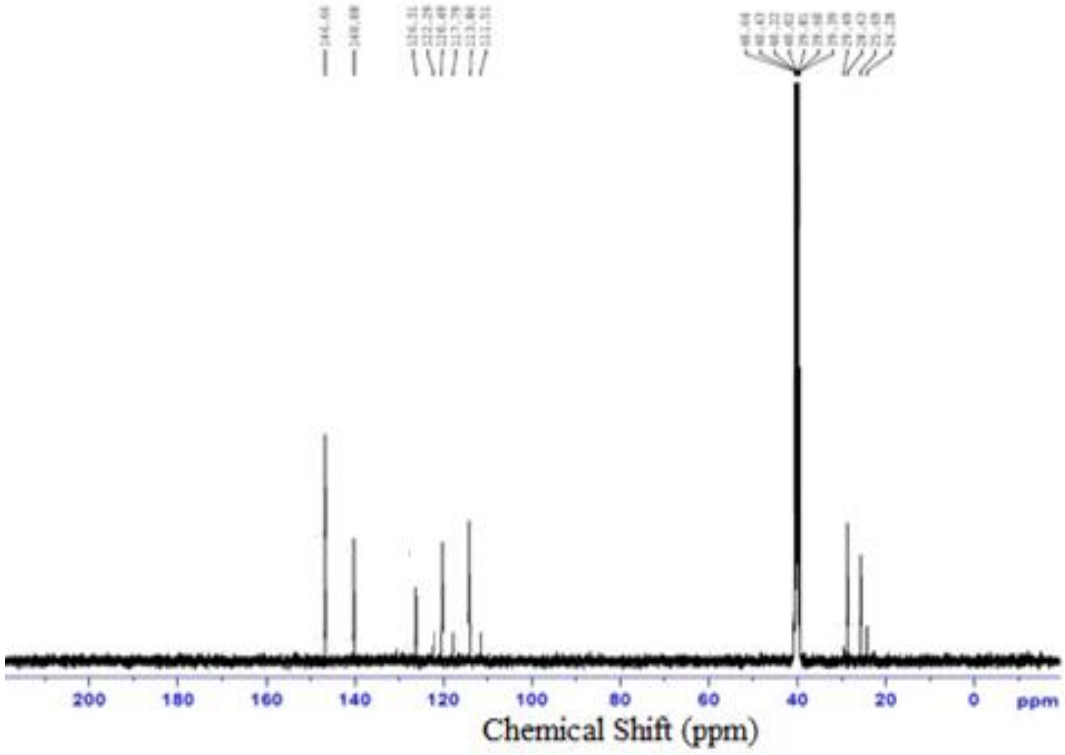


Figure 11: ^{13}C NMR spectrum of 6-Bromo-1,2,3,4-tetrahydrocyclopenta[b]indole.

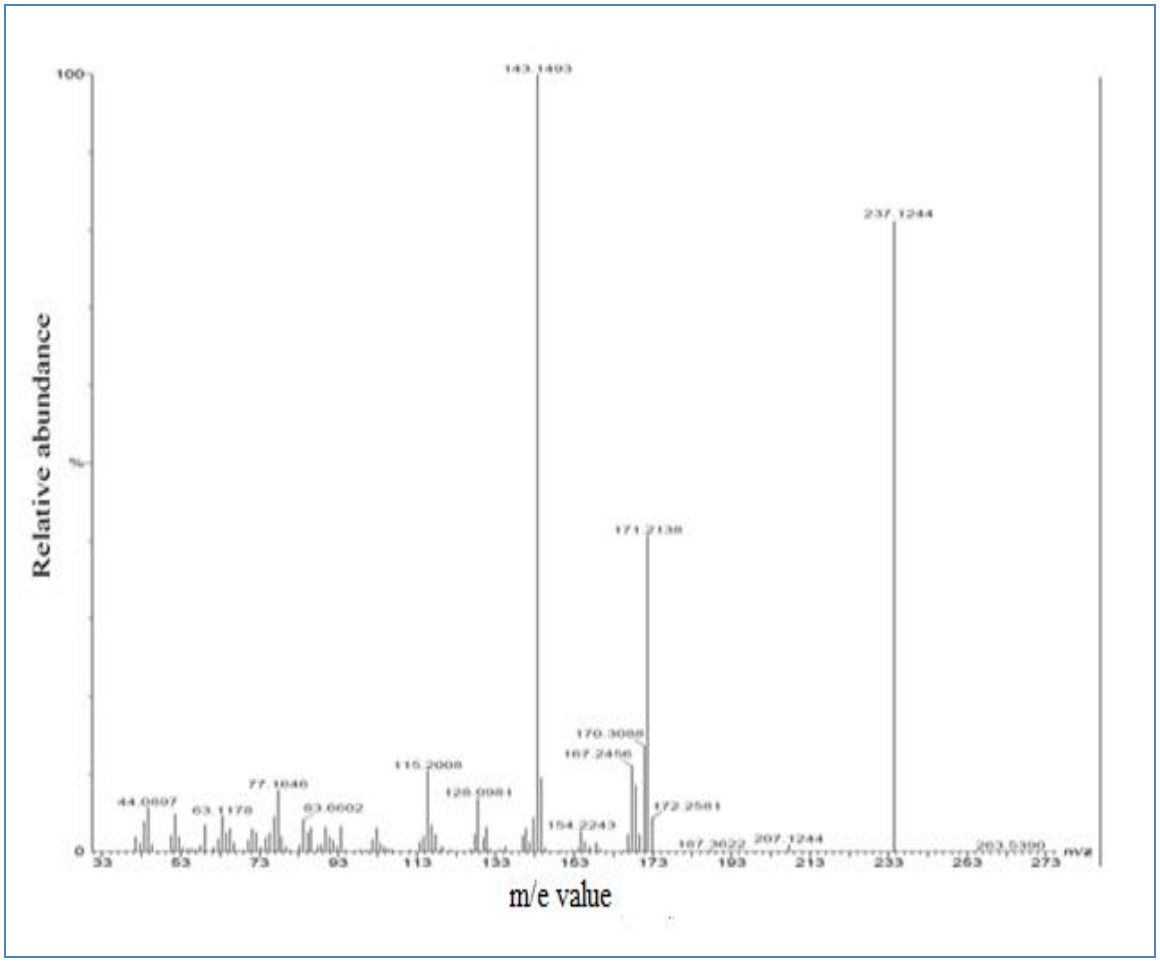


Figure 12: Mass spectrum of 6-Bromo-1,2,3,4-tetrahydro cyclopenta[b]indole.

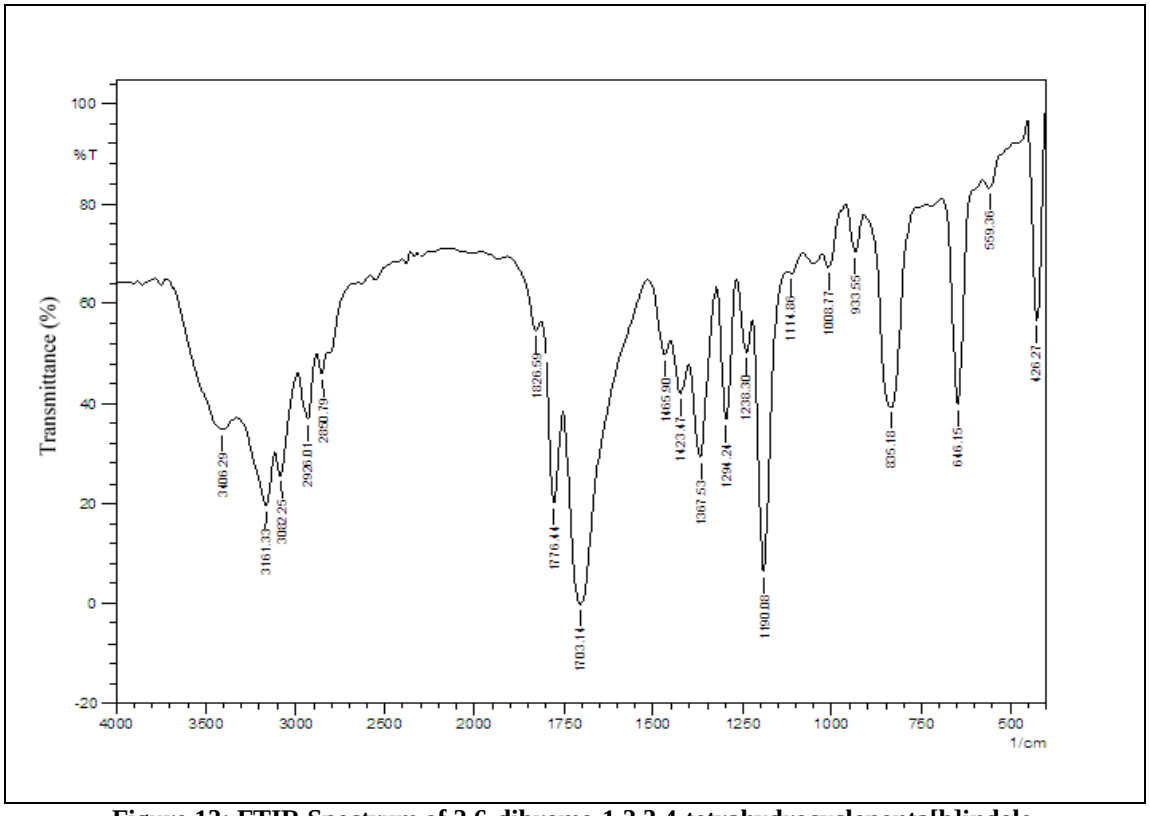


Figure 13: FTIR Spectrum of 2,6-dibromo-1,2,3,4-tetrahydrocyclopenta[b]indole.

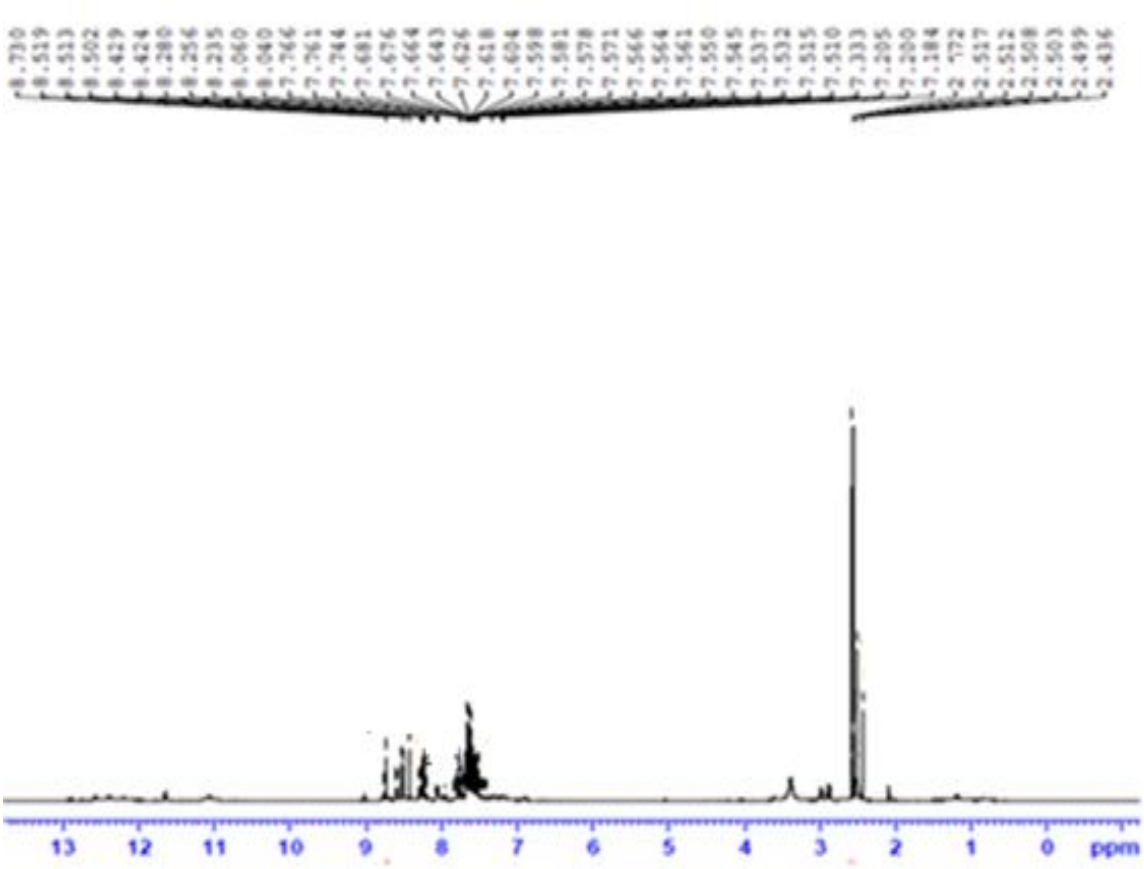


Figure 14: ^{1}H NMR Spectrum of 2,6-dibromo-1,2,3,4-tetrahydrocyclopenta[b]indole.

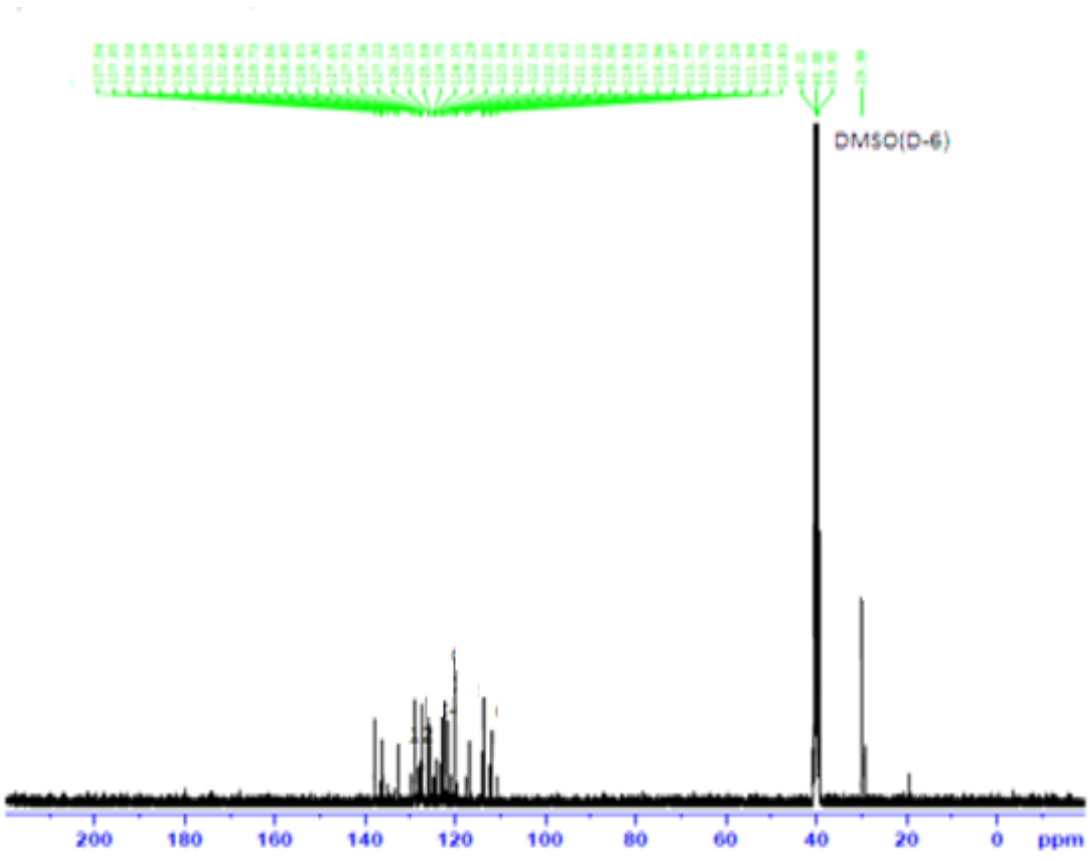


Figure 15: ^{13}C NMR Spectrum of 2,6-dibromo-1,2,3,4-tetrahydrocyclopenta[b]indole.

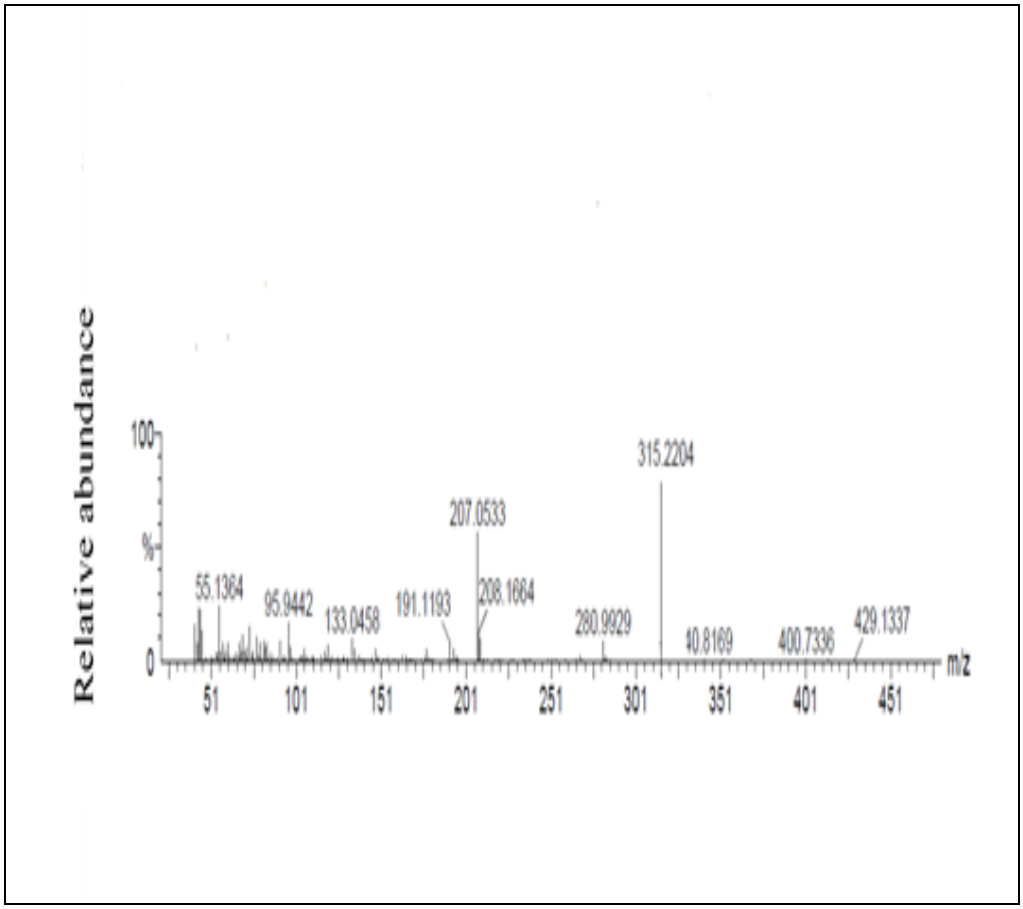
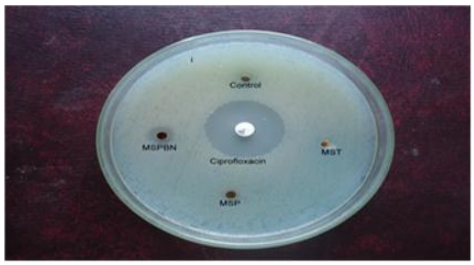
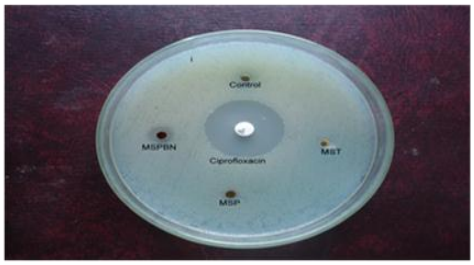


Figure 16: Mass Spectrum of 2,6-dibromo-1,2,3,4 tetrahydrocyclopenta[b]indole.

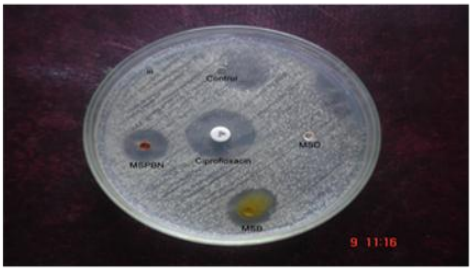
ANTIBACTERIAL ACTIVITY



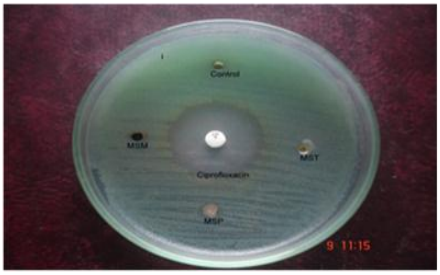
Pseudomonas aeruginosa



Bacillus species

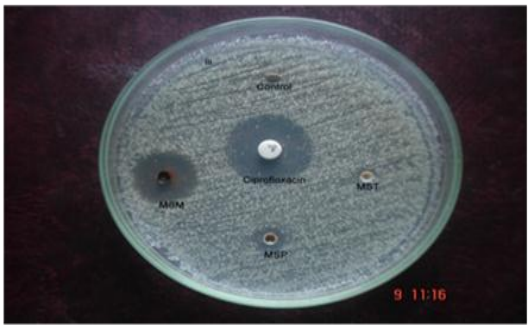


Staphylococcus epidermidis



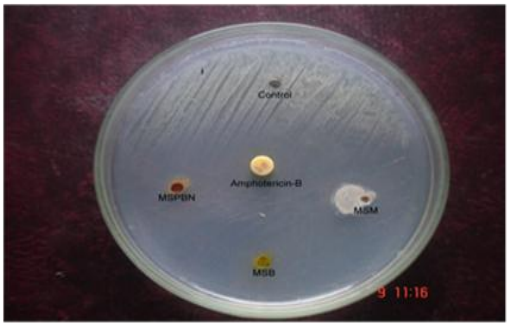
Pseudomonas aeruginosa

Bacillus species

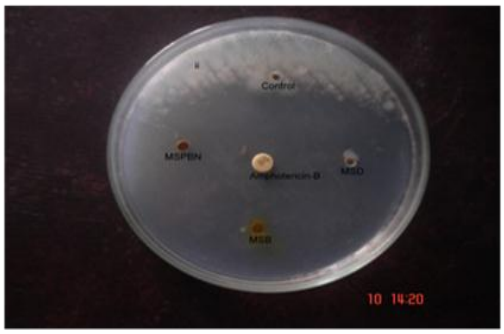


Staphylococcus epidermidis

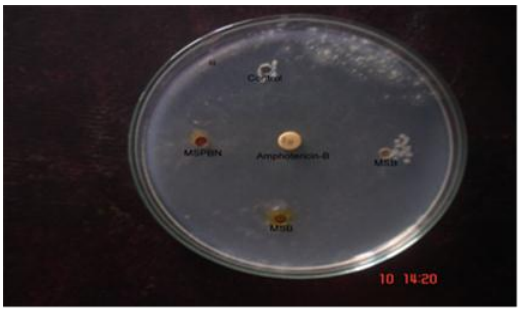
ANTIFUNGAL ACTIVITY



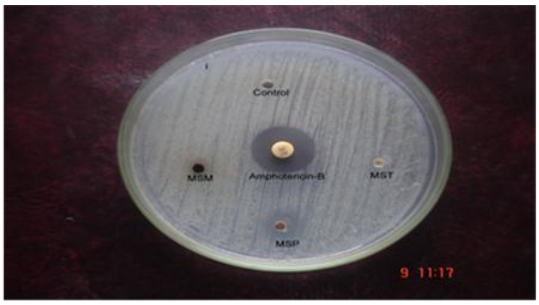
Candida tropicalis



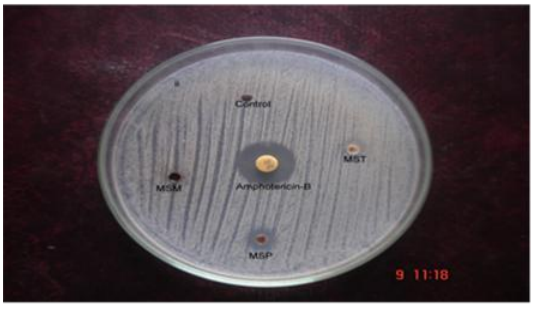
Aspergillus flavus



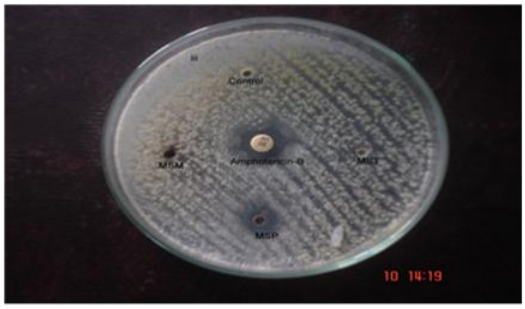
Aspergillus niger



Candida tropicalis



Aspergillus flavus



Aspergillus niger

Figure 17: Microbial activity.

2, 7-Dibromo 1,2,3,4-Tetra Hydro Cyclo Penta[b] Indole (2)

The FTIR spectrum was attributed to the band present at 3360cm^{-1} and 3238cm^{-1} have been assigned to N-H and =C-H stretching vibrations respectively. The band appeared at 2854-2922cm^{-1} was associated the aliphatic C-H stretching vibration. The stretching frequency appeared at 869 cm^{-1} corresponds to C-Br vibration in Fig 5. In the ^{1}H NMR (Fig 6) spectrum a singlet at 8.22, 8.16 ppm was due to N-H and aromatic singlet proton. For aromatic protons the multiplet signal appeared at 7.48 ppm-7.51ppm.The aliphatic protons appeared at 2.88-2.89ppm. the aliphatic multiplet proton appeared at 3.40-3.45ppm. Fig 7 indicates the ^{13}C NMR spectrum. In the ^{13}C NMR(DMSO d_6) predicts that the carbon atom present neighbouring to nitrogen atom has spectral value at 124,128ppm. The spectral value115-118ppm corresponds to aromatic carbons. The aliphatic carbon atoms had shown the spectral peak at 56.03(C-Br), 32.6 &29.5 ppm. The molecular ion peak of the compound was observed m/e ratio 315.1 in Fig 8.

6-Bromo-1,2,3,4-Tetra Hydrocyclopenta[b]Indole (3)

FTIR spectrum of 6-Bromo-1,2,3,4-tetrahydro cyclopenta [b] indole have shown in Fig 9. The intensity band at 3414 cm^{-1} observed due to the N-H stretching vibration. The medium at 2859 cm^{-1} have assigned to the aromatic =C-H stretching vibration.[31] The ^{1}H NMR spectrum of 6-Bromo-1,2,3,4-tetrahydro cyclopenta [b]indole shown in Fig 10. The chemical shift at 11 ppm was attributed to the N-H proton. The two doublets appeared at 7.05-7.24 ppm due to aromatic protons. The multiplet for four protons signal appeared 2.4-2.8 ppm denoted as aliphatic proton. The signal observed has triplet of two protons at 2.2-2.4 ppm.[32]

The compound 3 was also confirmed by using ^{13}C NMR spectrometer have shown in Fig 11. The aliphatic carbon atoms have shown the spectral peak at 25 ppm, 28 ppm and 29 ppm.The aromatic carbon signal appeared at 113-146 ppm.[33] The mass spectrum of the compound 3 shown in Fig 12. The molecular ion peak observed at m/z 237.12.

2,6-Dibromo-1,2,3,4-Tetrahydrocyclopenta[B]Indole (4)

Synthesis of the 2,6-dibromo-1,2,3,4-tetrahydrocyclopenta [b]indole have shown in scheme **2**. The FTIR spectrum of the compound **4** have shown in Figure **13**. The sharp intensity band at 3406 cm^{-1} was observed due to the N-H stretching vibration. The medium band at 3082 cm^{-1} were assigned to the aromatic =C-H stretching vibration. The band at 2850 cm^{-1} was observed due to aliphatic C-H stretching vibration. The sharp band appeared at 805 cm^{-1} was observed due to C-Br stretching vibration.

The ^{1}H spectrum of 2,6-dibromo-1,2,3,4-tetrahydrocyclopenta[b]indole have shown in Figure 14. A singlet at 8.730 ppm was due to N-H proton. A singlet appears at 8.502 ppm was due to aromatic singlet protons. A doublet appears at 7.626 ppm to 7.643 ppm corresponds to aromatic protons. A doublet appears at 2.512 ppm to 2.517 ppm corresponds to aliphatic protons. A multiplet appears at 2.436 ppm to 2.508 ppm corresponds to C-Br protons.

Compound **4** was also confirmed by using ^{13}C NMR spectrometer shown in Figure **15**. The peak appears at 29.99 ppm corresponds to aliphatic carbon atom. The peak appears at 111.14-133 ppm corresponds to aromatic carbon atoms. The mass spectrum of compound **4** have shown the Figure **16**. Observed Molecular ion peak at m/z 315.

Comparative Study of Antimicrobial Activity

The synthesized compounds were tested for microbial activity have shown in **Fig 17**.

Antibacterial activity

The results of antibacterial activity of synthesized compounds **2 & 4** was shown in table **1**. The zone of inhibition was indicated the nature of antibacterial activity. The synthesized compounds were subjected to *pseudomonas aeruginosa, Bacillus species and staphylococcus epidermidis.* Compound **4** shows zone of inhibition indicates that the compound shows good antibacterial activity.

Antifungal activity

The results of antifungal activity was shown in table **2**. The synthesized compounds were subjected to *Candida tropicalis*, *Aspergillus flavus* and *Aspergillus niger*. Compound **4** found to have excellent activity against all three fungi.

CONCLUSION

The expected bromo indole derivatives **2** & **4** were synthesized by enhanced fischer indole synthesis using phenyl hydrazine and reactant such as cyclopentanone followed by electrophilic bromination using NBS/H_2SO_4. The solvent selected must be suitable for reaction condition and temperature. The synthesized compounds have been confirmed by various spectral techniques viz UV, FTIR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy. The result of antimicrobial evaluation shows that the synthesized compounds found to have excellent antifungal activity than antibacterial activity.

REFERENCES

1. E.J. Stocks and G.L. Ridgway, Clinical Bacteriology, 5th Ed, Edward Arnold Ltd., 1975; 211.
2. J.G.Colleu, A.G Frances, B.P. Marmion and A. Simons, Mackei Mc.Cartney,14th Ed, London., 1996; 715
3. Indumathi, T., Brant, T., Zeller, M. and Rajandra Prasad, K.J. J. Ind. Chem, 2013; 4005-4013.
4. Barbieri, V. And Ferlin, M G. Tetrahedron Lett., 2006; 47: 8289-8292.

5. Chakrabarthy, M., Ghosh, N. and Harigaya, Y.A. (2004), Tetrahedron Lett., 45: 4955-4957.
6. Henon, H., Anizon, F., Golsteyn, R. M. Et al. Bio org. Med. Chem, 2006; 14: 3825-3834.
7. Fousteris, M A., Papakyriakou, A. and Koutsourea, A. et al. J Med. Chem, 2008; 51: 1048-1052.
8. Conchou, E., Anizon, F.and Aboad, B. Et al. J. Med. Chem, 2008; 43: 282-292.
9. Guilonneau, C., Pierre, A. and Charton, Y. Et al. J. Med. Chem, 1999; 42; 2191-2203.
10. Huang, F C., Chang, C C. And Lou, PJ. et al. Molcancer Res., 2008; 6: 955-964.
    Hudkins, R L., Diebold, JI., Angeles, T S. and Knight, E. J.Med. chem, 1997; 40: 2994-2996.
11. Malapaka, Ch., Gahugula, R., Thogot,S., chikkam, S.R., Paidi, X. R., Jun-HO, Y.,Mohammad,K. N., and Michael, G., 2001; 1-10.
12. Parler, S.P., ed. Macraw. Hill Bool.co. New York, NY, 1997; 67.
13. Robinson, B.The Fischer indole synthesis; Wiley & Sons: New York, 1982.
14. He, L.; Chang, H-X; Chou, T-C.; Savaraj, N.; Cheng, C. Eur.J. Med. Chem, 2003; 38-101.
15. Wiley, P. E. Verdazyls. Willey & Sons: New York, 1978; 1225-1246.
16. Elguero, J. Katritzky, A.R.; Rees, C. W., Scriven, E. F.V., Eds.; Pergamon, 1996; 3: 1-75.
17. Neugebawer, F. A.; Umminger, I. Chem. Ber., 1980; 113: 1205.
18. A.K. Mohanakrishnan, V. Dhayalan, J.A. Clement, R.Balamurugan, R. Sureshbabu and N. Senthil kumar, Tetrahedron. Lett, 2008; 49: 5850.
19. Humphrey, G. R. And Kuethe, J. T., Chem. REV., 2006; 106: 2875-2911.
20. Fischer, E.; Jourdan, F. Indole synthesis. Chem. Ber., 1883; 16: 2241.
21. Robinson, B. The Fischer indole synthesis Chem. Ber, 1963; 63: 373-401.
22. Van orden, R. B.; Lindwell, H.G. Indole, Chem. Rev., 1942; 30: 69-96.
23. M.F. Roberts, M. Wink (eds). New York, N Y, 1998.
24. A.L. Wilkins,C.O. Miles, R.M. Ede, R.T.Gallagher, S.C. Munday, J. Agric. Food chem., 1992; 40: 1307.
25. J.Bergman, L. Vene malm, A. Gogoll, Tedrahedron, 1990; 46: 6067.
26. A. Gopalsamy, M. Shi, G. Ciszewski, k. Park, J. W. Ellingboe, M. Orlowski, B. Feld, A. Y.M. Howe, Bioorg Med. Chem. Lett., 2006; 16; 2532.
27. A. L. Saab, R. L. Vogel, G.S. Welmaker, J. E. Sabalski, J. Coupet, J. Dunlop, S. Rosenzweig-Lipson, B. Harrison, Bio org, Med. Chem. Lett., 2004; 10: 2603.
28. Frφyen, P. Phosphoru Sulfur, 1995; 102: 252-259.
29. Cho HN, Kim DY, Kim YC, Lee JY, Kim CY Adv. Mater, 1997; 9: 326.
30. Navin Turan., J. C. Patel, and G. G. Barat. "Synthesis and Antimicrobial Activity of 2-[2-(2, 6-dichloro phenyl) amino] benzyl-3-(5-substituted phenyl-4, 5-dihydro-1H-pyrazol-3-yl-amino)-6, 8-dibromoquinazolin-4 (3H) ones." *Journal of Young Pharmacists* 2.2, 2015; 173-182.
31. Armin de Meijere, Ligang Zhao and Stefan W. Hell., Chem. Eur. J., 2007; 13: 2503-2516.
32. Cuihua Xue and Fen-Tair Luo, Tetrahedron, 2004; 60: 6285-6294.