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SYNTHESIS OF BIOLOGICALLY ACTIVE BROMO DERIVATIVE OF [b] CARBAZOLE BY AN ELECTROPHILIC AND FREE RADICAL BROMINATION

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ABSTRACT

The prevalence of heterocycles in medicinally important compounds continues to derive the need for new methods for their preparation. Carbazole derivatives are known to have important biological properties. 5,9-Dibromo-6,11-dihydro-5H- benzo [α]carbazole was prepared in good yield by an electrophilic bromination using NBS/ con.H_2SO_4. The synthesized compound were characterized and confirmed by FTIR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy. The synthesized compounds were carried out under antibacterial evaluation. The results showed that the synthesized compounds exhibit good antibacterial activity.

KEYWORDS: Alpha tetralone, N-bromo succinimide, Con. Sulphuric acid, Ciprofloxacin, 5,9-dibromo-6,11-dihydro-5H- benzo [a]carbazole.

INTRODUCTION

Heterocyclic compounds are widely distributed in nature and occupy a prominent place in medicinal chemistry as pharmaceuticals and drug intermediates. They play a significant role in the metabolism of all living cells and many are clinical use for the treatment of various diseases. Nitrogen containing heterocyclic such as indole or carbazole are probably the most widely spread nitrogen heterocycles in nature[i]. A survey of the pertinent literature revealed that carbazole have been found to possess a wide spectrum of biological activity such as antibacterial [ii], antirheaumatoid arthritis [iii], antitubercular [iv], antiviral [v], antiepileptic [vi], anti-inflammatory [vii], and anti-cancer [viii-ix] activities.

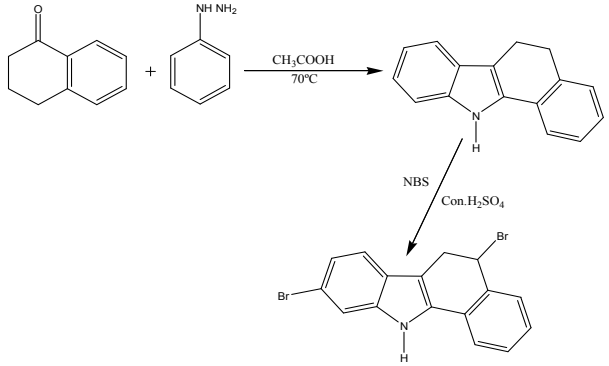
Development of new methods for the synthesis of heterocyclo – fused carbazole is currently attracting the organic chemists due to the discovery of many compound alkaloids with varied biological activities [x]. Ever since, the first isolation of a carbazole alkaloid, organic chemists have been interested in the synthesis of carbazole and its derivatives due to their promising biological activities. Recently Knolker and Reddy extensively reviewed the synthesis of biologically active carbazole alkaloids [xi].

In spite of reporting various methods for the synthesis of indoles,[xii] Fischer indole synthesis is probably the most widely investigated synthesis of indole and carbazole derivatives.

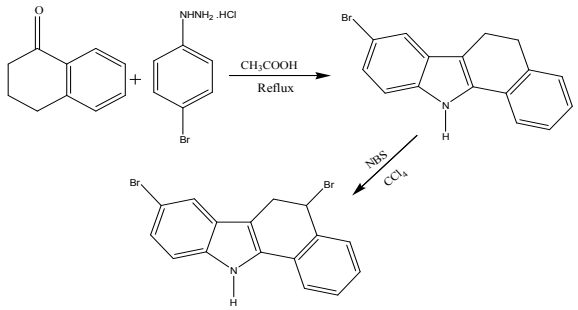
Alpha-tetralone serves as an important source of synthetic precursors for a wide range of compounds, including steroids, heterocycles, and pharmaceuticals [xiii]. While the 1-tetralones are inexpensive, easily prepared and commercially available, the 2-tetralones are often very expensive and much more difficult to synthesize. Carbazoles and benzo carbazoles have recently attracted much attention as proven or potential carcinogens. Dibenzo (a,g) carbazole also possess considerable inhibitory powers against the growth of Walker rat carcinoma [xiv].

Benzo dihydro(α) carbazole has been reported as a primary compound for the synthesis of various drugs and possesses important biological, pharmacological and medicinal activities. BDHC is associated with anti cancer, anti microbial and anti fungal activities [xv]. In most cases, biological activity is correlated with BDHC containing heteroatoms which depends on the interaction potential with DNA. Furthermore, many experimental studies have indicated that the size, shape and planarity of this structure are important criteria in such an interaction.

While ***N***-Bromosuccinimide (NBS) is a convenient source of bromine for both substitution and electrophilic addition reactions. NBS has been extensively used for allylic and benzylic bromination. Bromination is a very important process in organic synthesis as bromo derivatives serve as useful intermediates in the manufacture of pharmaceuticals, agrochemical and other specialised chemicals. [xvi] Moreover, many pesticides, insecticides, herbicides and fire retardants contain the bromine functionality. [xvii-xviii] *N*-Bromosuccinimide is one of the most pronozing brominating agents, especially for free radical bromination. These results motivated to synthesis of different types of indoles. Herein, the present investigation delineate a general and facile approach for the construction of bromo derivatives of heterocyclo [b] carbazole.



Scheme 1. Synthesis of 2,6-dibromo-5,6-dihydro-11H-benzo[α]carbazole.



Scheme 2. Synthesis of 3,6-dibromo-5,6-dihydro-11H-benzo[α]carbazole.

RESULT AND DISSCUSSION

5,6-dihydro-11H-benzo[α] carbazole

In the FTIR spectrum of 5,6-dihydro-11H- benzo[α]carbazole, the characteristic frequency of the aromatic keto group at 1740 cm^{-1} was not present in the spectrum, which indicated the formation of indole. The sharp intensity band at 3412 cm^{-1} was observed due to the N-H stretching vibration. The medium band at 3026 cm^{-1} were assigned to the aromatic =C-H stretching vibration. The sharp band appeared at 2939 cm^{-1} was associated the aliphatic C-H stretching vibration. In the ^{1}H NMR spectrum of compound, a singlet at 10.3 ppm was due to N-H proton. The doublet signal appeared at 7.49 ppm corresponds to aromatic protons. The two doublet signals appeared at 6.9 ppm – 7.0 ppm equivalent to two protons. For four aromatic protons the multiplet signal appeared at 6.90 ppm-7.28 ppm. The signal observed has multiplet for four protons at 2.9 ppm-3.0 ppm. In ^{13}C NMR spectra, signals appeared at 110 ppm-129 ppm confirms the presence of aromatic carbons. The carbon present at the condensed position appeared at 133 ppm and 135 ppm. The carbon signal observed at 145 ppm and 138ppm corresponds carbons which were near to nitrogen atom. The aliphatic carbon signals appeared at 21.9 ppm and 19.2 ppm**.** The mass spectrum of synthesized compound shows the molecular ion peak was observed at m/z 218.2.

3-bromo-5,6-dihydro-11H-benzo[α]carbazole

Figure 5 shows the FT-IR spectrum of the synthesized compound. The sharp intensity band at 3433 cm^{-1} observed due to the N-H stretching vibration. The medium at 2924 cm^{-1} assigned to the aromatic =C-H stretching vibration. The sharp band appeared at 2852 cm^{-1} associated the aliphatic C-H stretching vibration.The ^{1}H NMR spectrum of 8-Bromo-6,11-Dihydro-5-H-carbazole have shown in. The chemical shift at 11.6 ppm attributed to the N-H proton. The multiplet signal appeared at 7.3-7.5 ppm corresponds to aromatic protons. For four aromatic protons two doublet signal appeard at 7.29 ppm. The muliplet appeared at 2.5-2.8 ppm was denoted by aliphatic protons**.** In the ^{13}C NMR spectra of compound the aliphatic carbon signals appeared at 29 ppm. In ^{13}C spectra signals at around 113 ppm ,116 ppm and 120 ppm confirms the presence of aromatic carbons. The carbon present at the condensed position signals appeared at 124 ppm 135 ppm**.** The mass spectrum of the compound have shown the molecular ion peak m/z 297.1. The calculated mass value found to have m/z 298.1.

2,6-dibromo-5,6-dihydro-11-H-benzo[α]carbazole.

The FTIR spectrum of the 2,6-dibromo-5,6-dihydro-11-H-benzo[α]carbazole indicates the strong absorption at 3420 cm^{-1} owing to the N-H stretching vibration in hetero aromatic system. The strong C-Br stretching at 756 cm^{-1} indicates the presence of bromo group. The ^{1}H NMR spectrum of the compound 2 have shown a singlet at 12.5 δ appeared due to the N-H proton. The peak assigned at 7.97 δ equivalent to1H singlet. The triplet centered at 2.93-2.95 δ and doublet at 2.04- 2.05δ.. The ^{13}C NMR (DMSO-d_6) exhibited aliphatic carbon with (del value) at 22 ppm, Aliphatic carbon containing bromine (C-Br) at 38.0ppm, Aromatic ring carbon was observed between 116-137 ppm. The mass spectrum of the compound appeared at m/z 375 , 377 (M+2) .

3,6-dibromo-5,6-dihydro-11-H-benzo[α]carbazole.

Synthesis of the 5,8-dibromo-5,6-dihydro-11-H-benzo[α]carbazole have shown in Scheme **2**. The FTIR spectrum of the compound have shown sharp intensity band at 3425cm^{-1} was due to the N-H stretching vibration. The medium band at 3061cm^{-1} were assigned to the aromatic =C-H stretching vibration. The band at 2852 cm^{-1}due to the aliphatic C-H stretching vibration. The sharp band at 746cm^{-1} was observed due to C-Br stretching vibration.

The ^{1}H spectrum of 5,8-dibromo-5,6-dihydro-11-H-benzo[α]carbazole have shown a singlet at 8.580 ppm was due to N-H proton. The chemical shift value appeared at 7.505 to 8.457 corresponds to aromatic protons. The triplet appeared at 5.305 ppm to 5.332 ppm corresponds to the proton (C-Br). Formation of compound have also confirmed by ^{13}C NMR spectrometer. A aliphatic carbon atoms have shown the peak at 55.80 and 29.99 ppm. The peak appears at 125.3 to 133.4 ppm corresponds to aromatic carbon atoms. The mass spectrum of the compound was assigned to the molecular ion peak at m/z 375.19 and M+2 peak was observed at 377.00 due to the presence of bromine.

Antibacterial activity

The results of antibacterial activity of synthesized compound have presented 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.* Based on the survey of the antibacterial activity, among all, the compound **2** found to have excellent antibacterial activity.

Antifungal activity

The results of antifungal activity have shown in Table **9**. The synthesized compounds were subjected to *Candida tropicalis, Aspergillus flavus* and *Aspergillus niger*. Compound **2** found to have excellent activity against all three fungi.

EXPERIMENTAL SECTION

Synthesis of 5,6-dihydro-11H-benzo[α]carbazole

6N-Sulphuric acid (5.14ml), water (48.8ml) and phenyl hydrazine (2.46g, 0.023mol) were stirred under reflux. Alpha-tetralone (0.023mol, 3.33g) was added dropwise during 5 minutes and the mixture stirred under reflux for 2 hours, then cooled to 20℃ and extracted with ethyl acetate and water have shown in scheme 1. Removal of the solvent and purification of a portion of the residue through a column of silica gel with methylene chloride: hexane (2:10, v/v) as eluent resulted in yellow solution, which slowly solidified.

Yield :70% ,Melting point 228-230℃, FTIR(KBr):3412cm^{-1}(N-H), 3026cm^{-1}(C-H aromatic), 2939cm^{-1}(C-H aliphatic) , 1589cm^{-1} (C=C). ^{1}H NMR(DMSO d^{6}), ppm) :10.3(s,N-H), 7.4 (2d, 2H), 6.9-7.0 (2d,2H), 2.9-3.0 (2d,2H) , 7.24-7.28(m, 2H) &6.90-6.94 (m, 2H).^{13}C NMR(DMSO d^{6}):110, 125, 135, 145 &19. Mass spectrum :M/Z ratio 218.2.

Synthesis of 3-bromo-5,6-dihydro-11H-benzo[α]carbazole

The synthesis of 3-bromo-5,6-dihydro-11H-[α]carbazole was achieved from alpha tetralone (3.3mmol, 0.4897g) and 4-Bromo Phenylhydrazine hydrochloride (3.3mmol, 0.7487g) using glacial acetic acid (10ml) as a solvent at 70 ºC. The addition of 4-bromophenylhydrazine hydrochloride was taken an interval of 30 minutes. When the addition was completed the content was heated to reflux with constant stirring of about 3 hours. Then the reaction mixture was poured into ice cold water with constant stirring. The pure solid was formed which was separated by filtration and the precipitate was washed with water and dried. The desired compound B was obtained in good yield. Obtained pale yellow product were recrystallized in methanol.

Yield :90% ,Melting point 202-204℃, FTIR(KBr): (N-H, st) 3433 cm^{-1}, (=C-H,st) 2924 cm^{-1}, (C-H,st) 2852 cm^{-1}, (C=C,st) 1462 cm^{-1}, (C-N,st) 1381 cm^{-1}, (C-C,st) 1240 cm^{-1}, (C-Br,st) 723 cm^{-1} .^{1}H NMR(DMSO d^{6}), ppm) : 7.3-7.5(m,2H), 7.17-7.19(2d,2H), 7.29(2d,2H), 2.5-2.8(m,4H), 8.42-8.49(s,H), 11.6(S,N-H). ^{13}C NMR(DMSO d^{6}):113-137, 29&19. Mass spectrum :M/Z ratio 297.1.

Synthesis of 2,6-dibromo-5,6-dihydro-11-H-benzo[α]carbazole.

N- bromosuccinimide (NBS) (10.82 g, 0.06 mol) was slowly added to a solution of 5,6-dihydro-11-Hbenzo[a]carbazole (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 taken in a beaker, and stirred well. The 2,6-dibromo-5,6-dihydro-11-H benzo[a]carbazole was purified using hot ethanol and further purification by recrystallization from ethyl acetate afforded a dark maroon powder.

Yield : 82% ,Melting point 185-190, FTIR(KBr): (N-H Str)3420cm^{-1}, (=C-H Str) 3038cm^{-1} , (C-H Str) 2858-2924cm^{-1} ,(C=C Str) 1654cm^{-1}, (C=C-Br Str) 1448cm^{-1}, (C-Br Str) 756cm^{-1} , NMR(DMSO d^{6}), ppm : 12.5ppm(S ,N-H), 7.97ppm(S,H), 7.34-8.95ppm(Ar,H-m), 2.93-2.95ppm(t,2H), 2.04-2.05ppm(d,H). ^{13}C NMR(DMSO d^{6}):116-137, 38&22. Mass spectrum :M/Z ratio 375, 377(M+2). .

Synthesis of 3,6-dibromo-5,6-dihydro-11-H-benzo[α]carbazole.

The round bottom flask was charged with (0.7902g, 0.00265mole) of 8-bromo-5,6-dihydro[3,2-a]carbazole, (0.4717g, 0.00265mole) N-bromo succcinimide and 10mg of benzoyl peroxide has free radical initiator in 25ml of carbontetrachloride. The reaction mixture was allowed to reflux with constant stirring for 24 hours and the refluxing temperature was maintained to 70-75°C. The progress of the reaction mixture was monitored by TLC. The reaction mixture was filtered, and evaporate the filterate to afford yellow crystals of the product. The 85-90% of yield were obtained. The melting point of synthesized compound found to have is

Yield : 82% ,Melting point 180-182°C, FTIR(KBr): N-H-3425cm $^{-1}$, =C-H-3061cm$^{-1,}$ C-H-2852cm$^{-1,}$C-Br-433cm$^{-1,}$ ^{1}HNMR(DMSO d^{6}), ppm: N-H-8.580 s, (8.457-8.479, d), (8.088-8.108, d)**,** (7.507-7.601, m), (5.453-5.466, d), (5.305-5.332, t), ^{13}C NMR(DMSO d^{6}):125-133, 55&29. Mass spectrum :M/Z ratio 375, 377(M+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.

CONCLUSION

The bromo derivatives of [b]carbazole has been achieved by free radical and electrophilic bromination using N-bromosuccinimide as a bromine source. All the synthesized compounds have been 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.

METHODS AND MATERIALS

All the reagents used were purchased from Merck and Aldrich and used without further purification.

The melting points of synthesized compounds were determined by open capillary tubes using an X-5A Melting point apparatus and were uncorrected. Thin layer chromatography among to

most useful tools for following the progress of organic chemical reaction and for assaying the purity of organic compounds. FTIR spectra was 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 downlfield 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.

CONFLICT OF INTEREST

The authors confirm that this article do not have any conflict of interest.

REFERENCES

i. Indumathi ,T., Brant, T., Zeller,M . and Rajandra Prasad ,K.J.(2013) ," Synthesis and antibacterial evaluation of bromo phenyl substituted carbazoles",J. Ind. Chem. 4005-4013.

ii. Barbieri , V. And Ferlin , M G.(2006). "Synthesis of 3-(quinolin-2-yl)- and 3,6-bis(quinolin-2-yl)-9*H*-carbazoles",Tetrahedron Lett.47 : 8289-8292.

iii. Chakrabarthy , M., Ghosh , N . and Harigaya , Y.A. (2004), "Recent Developments and Biological Activities of *N*-Substituted Carbazole Derivatives",Tetrahedron Lett. 45: 4955-4957.

iv. Henon , H., Anizon ,F., Golsteyn , R. M. Et al.(2006) "Synthesis and biological evaluation of new dipyrrolo[3,**4**-α:3,**4**-c]carbazole-. 1,3,**4**,6-tetraones, substituted with various saturated and unsaturated side chains via palladium catalyzed cross- coupling reactions". Bio org . Med. Chem. . 14: 3825-3834 .

v. Fousteris , M A ., Papakyriakou , A. and Koutsourea , A . et al .(2008) Identification of 4,**5**-Dihydro-1H-pyrazolo[4,3-h] quinazoline Derivatives as a New Class of Orally and Selective Polo-Like Kinase 1 Inhibitors" .. J Med. Chem. . 51: 1048-1052 .

vi. Conchou , E., Anizon , F. and Aboad , B. Et al . (2008). "Synthesis, in- vitro antiproliferative activity and chk1 inhibitory properties of pyrrolo [3,4-α] pyrrolo [3,4-c] carbazole 1,3-diones and 2- aminopyridazino. [3, 4- α] pyrrolo. [3,4-c] carbazole-1,3,4,7-tetraone". J . Med. Chem. 43: 282-292.

vii. Guilonneau , C ., Pierre , A. and Charton , Y. Et al. (1999) "Corticotropin Releasing Factor (CRF) Agonists with Reduced Amide Bonds and Ser Substitutions".J. Med . chem.. 42; 2191-2203.

viii. Huang , F C ., Chang, C C. and Lou, PJ . et al . (2008) "G-quadruplex stabilizer 3,**6**-bis(1-methyl-4-vinylpyridinium) carbazole diiodide induces accelerated senescence and inhibits tumorigenic properties in cancer cells".. Molcancer Res. 6: 955-964.

ix. Hudkins , R L ., Diebold ,JI ., Angeles , T S . and Knight , E .(1997), " Fused enhance human interferon activity" J.Med. chem..40:2994-2996.

x. V. Sangeetha, and K. J. Rajendra Prasad, "Syntheses of novel derivatives of 2-acetylfuro[2,3-a] carbazoles",Indian . J. Chem ., 45 B, 1951 (2006).

xi. A.K. Mohanakrishnan , V. Dhayalan ,J.A. Clement , R.Balamurugan , R. Sureshbabu and N. Senthil kumar , "Synthesis and characterization of benz-annelated thienyl oligomers"Tetrahedron. Lett., 49, 5850 (2008).

xii. Humphrey , G. R. And Kuethe , J. T., Chem. REV., "*N*-Heterocyclic Carbene-Catalyzed Synthesis of 2-Aryl Indoles", 106; 2875-2911 (2006).

xiii. Ye, B.; Yao , Z.J.; Burke, T.R. "Aerobic a -hydroxylation of b-keto esters and

amides" J.Org. chem 1997, 62,5428.

xiv. Ng . Ph .Buu –Hoi, Ng Hoan and Ng .H.Khoi, "the reaction of diarylformamidines with ethyl malonate", J. Org. Chem.. 14.492(1949).

xv. Segall , A.; Pappa ,H. ;Pizzorno, M . T. Radice , M .; Amoroso, A.; Gutkind , G. IL Farmaco "docking studies of inhibition activity of. 5,6-dihydro 11-alkylbenzo[α]carbazole derivatives against estrogen receptor". 1996, 51, 513-516.

xvi. Waki, Y.; Tanaka, "Palladium-Catalyzed Tetrakis(dimethylamino)ethylene-Promoted Reductive Coupling of Aryl Halide"s, H.J. Org. Chem. 2003, 68, 3938-3942.

xvii. Walker,J. "Marine haloperoxidases" , Chem. Rev. 1993, 93, 1937-1944.

xviii. Gribble, G. "The diversity of naturally occurring organobromine compounds", Chem. Soc. Rev. 1999, 28, 335-346.

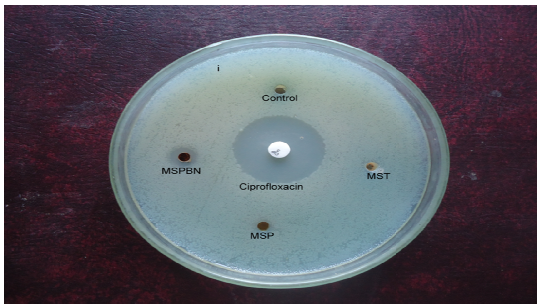
Zone of inhibition of antibacterial activity:

Compound	**ZONE OF INHIBITION**					
	Pseudomonas aeruginosa		***Bacillus species***		***Staphylococcus epidermidis***	
	mm	%	mm	%	mm	%
Ciprofloxacin	20	100	22	100	30	100
Sample 1	8	40	10	45	14	46
Sample 2	10	50	12	54	12	40

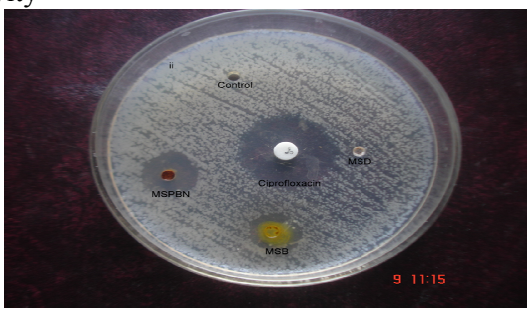
Zone of inhibition of antifungal activity:

Compound	**ZONE OF INHIBITION**					
	Candida tropicalis		***Aspergillus flavus***		***Aspergillus niger***	
	Mm	%	mm	%	mm	%
Amphotericin-B	20	100	100	100	100	100
Sample 1	40	100+	30	30	100	100
Sample 2	35	100+	28	28	90	90

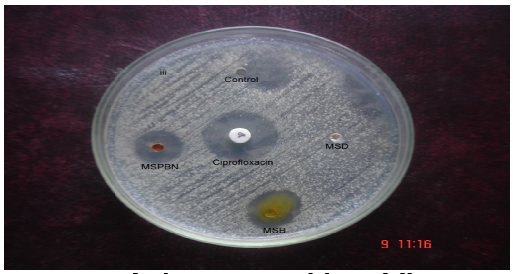
ANTIMICROBIAL ACTIVITY-antibacterial activity



Pseudomonas aeruginosa

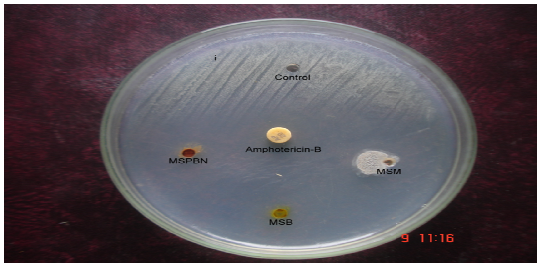


Bacillus species

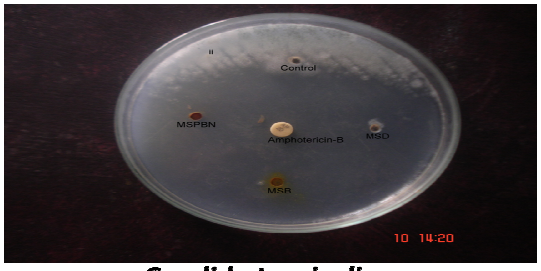


Staphylococcus epidermidis

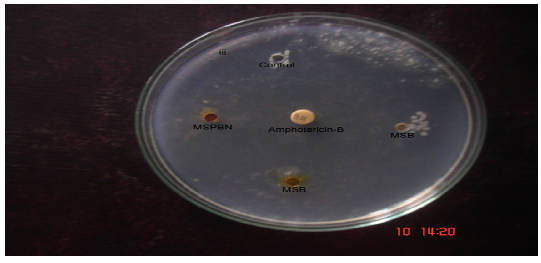
ANTIFUNGAL ACTIVITY



Aspergillus niger



Candida tropicalis



Aspergillus flavus

MICROBIAL ACTIVITY