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Synthesis And Antimicorbial Evaluation Of Indole Derivatives

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ABSTRACT: *Heterocyclic compounds constitute the core structure of a number of biologically interested compounds against microorganisms. The synthesis of substituted and condensed indole has been attracted many researchers due to their importance in biological activity. So far, five compounds has been synthesized by enhanced approach of Fischer's synthesis namely 1,2,3,4-tetra hydrocyclopenta(b)indole, 3,8-dihydro-2H-furo(2,3-b)indole, 5,6-dihydro-11H-benzo(a)carbazole, 6,11-dihydro diindolo(3,2b)carbazole and 12,12-dimethyl-6-hydro-indolo (3,2-b)carbazole. The formation of various compounds were confirmed by spectral techniques viz, FTIR, ^{1}H NMR, ^{13}C NMR, MASS Spectroscopy. A comparative study among the compounds of present investigation on antimicrobial evaluation reveals that all the compounds exhibit excellent antifungal activity than antibacterial activity.*

Keywords: *Alpha-tetralone, sulphuric acid, phenylhydrazine, ciprofloxacin, amphotericin-B.*

I. INTRODUCTION

An indole is characterized as a benzene ring fused to a nitrogen-containing five membered heterocylic ring. The Fischer indole synthesis is the most widely used and versatile method for indole synthesis. The Fischer indole synthesis converts ayrlhydrazones of aldehydes or ketones into indoles in the presence of an acid catalyst. [1] The first indolization of an arylhydrazone was effected by the use of an alcoholic solution of hydrogen chloride**. [2]** Later, during an extention of the reaction, it was found that a more varsatile reagent for effecting indolization was anhydrous zinc chloride five time excess effectiveness when compared with normal catalyst like CH_3COOH. A variety of catalyst has been used to effect the indolization of arylhydrazones. Carbazole derivatives are well known for their pharmacological activites. These compounds have been reported to prossess diverse biological activity like antibacterial and antifungal activities. Carbazole derivatives like ellipticin, and alkaloids such as vincristine, vinblastine found to have a well established role in the treatment of cancer. [3,4 & 5]. A survey of the pertinent literature revealed that carbazole have been found to possess a wide spectrum of biological activity such as antibacterial [6], antirheaumatoid arthritis [7], antitubercular [8], antiviral [9], antiepileptic [10], anti-inflammatory [11], and anti-cancer [12-13] activities.

1.1 Alpha – teralone

The teralone family serves as an important source of synthetic precursors for a wide range of compounds, including steroids, heterocycles, and pharmaceuticals [14]. While the 1-tetralones **12** 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 [15]. Despite of synthetic activity in this general area, very few C-alkyl benzo carbazoles have previously been described. Benzo dihydro(α) carbazole (BDHC) 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 [16]. Herein, the present investigation delineate a general and facile approach for the construction of heterocyclo (b) fused carbazole.

II. EXPERIMENTAL SECTION

2.1. Methods and materials

Phenyl hydrazine, acetic acid and alpha-tetralone were purchased from Avra synthesis, pvt.Ltd., Hyderabad. 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.

2.2 Synthesis Of 5,6-Dihydro-11h-Benzo(A) 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.

2.3 Evaluation Of Antimicrobial Activities

2.3.1 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.

III. RESULT AND DISSCUSSION

5,6-dihydro-11h-benzo(a) carbazole

The FTIR spectrum of 5,6-dihydro-11H- benzo(a)carbazole figure1 shows the characteristic frequency due to the stretching 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. The ^{1}H NMR spectrum of compound figure 2 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 spectra figure 3 signals at around 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 compound figure 4 shows the molecular ion peak was observed at m/z 218.2.

Antimicrobial evaluation shows that the synthesized compound found to have good antifungal activity than antibacterial activity have shown in table 1 & table 2.

IV. CONCLUSION

The expected indole compounds **A, B, C, D** & **E** were synthesized by enhanced fischer indole synthesis using phenyl hydrazine and α-tetralone with suitable solvent. The synthesized compound have been confirmed by using various spectral techniques *viz* , FTIR, ^{1}H NMR, ^{13}CNMR and Mass spectrum.The synthesized compound found to have excellent antifungal activity than antibacterial activity.

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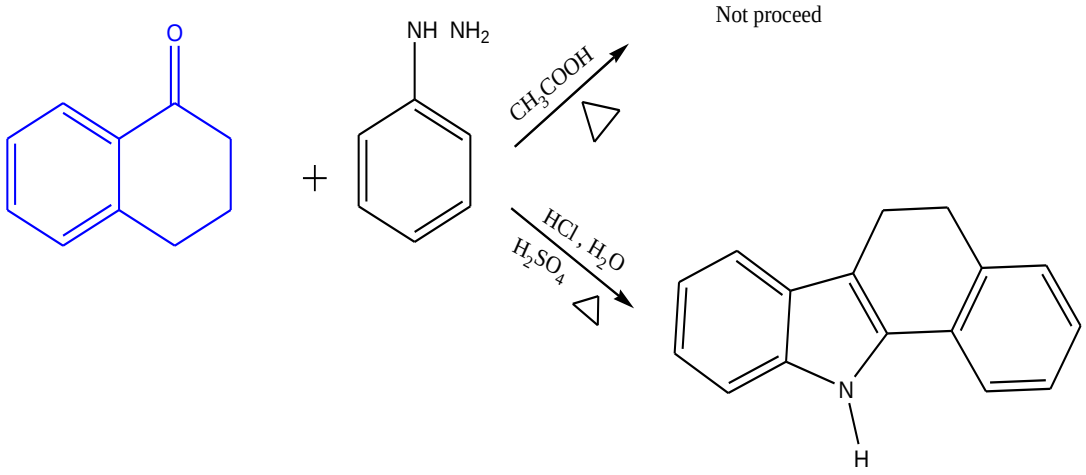
Scheme 1



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

Zone Of Inhibition Of Synthesized Compounds

Table 1 Antibacterial activity of synthesized compound

Compound	ZONE OF INHIBITION					
	Pseudomonas aeruginosa		*Bacillus species*		*Staphylococcus epidermidis*	
	Mm	%	Mm	%	mm	%
Ciprofloxacin	20	100	22	100	30	100
Compound	6	30	13	59.09	13	43.3

(-) = No antibacterial activity

Table 2 Antifungal Activity Of Synthesized Compound

Compound	ZONE OF INHIBITION					
	Candida tropicalis		*Aspergillus flavus*		*Aspergillus niger*	
	Mm	%	Mm	%	mm	%
Amphotericin-B	20	100	20	100	16	100
Compound	9	45	8	40	8	40

(-) = No antifungal activity

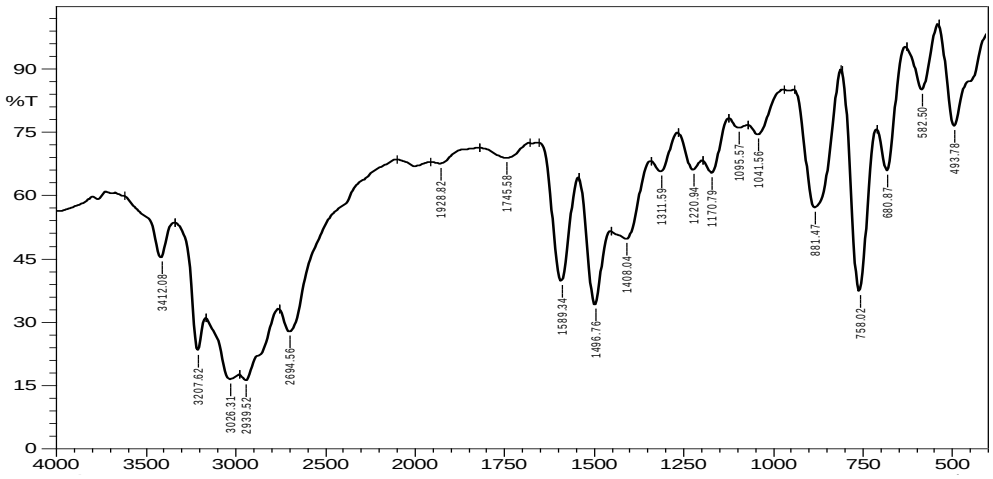


Figure 1. FTIR spectrum of 5,6-dihydro-11H-benzo(a)carbazole.

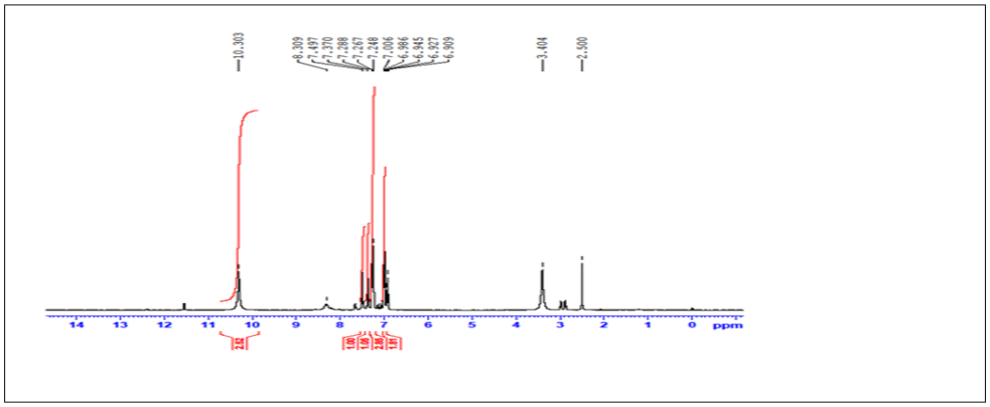


Figure 2. 1H NMR spectrum of 5,6-dihydro-11H-benzo(a)carbazole.

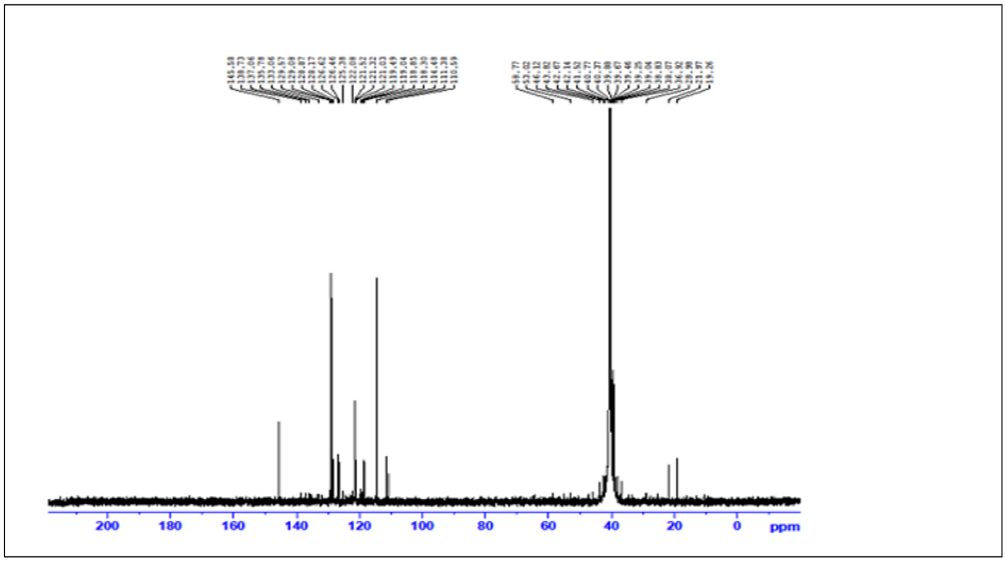


Figure 3. ^{13}C NMR spectra of 5,6-dihydro-11H-benzo(a)carbazole.

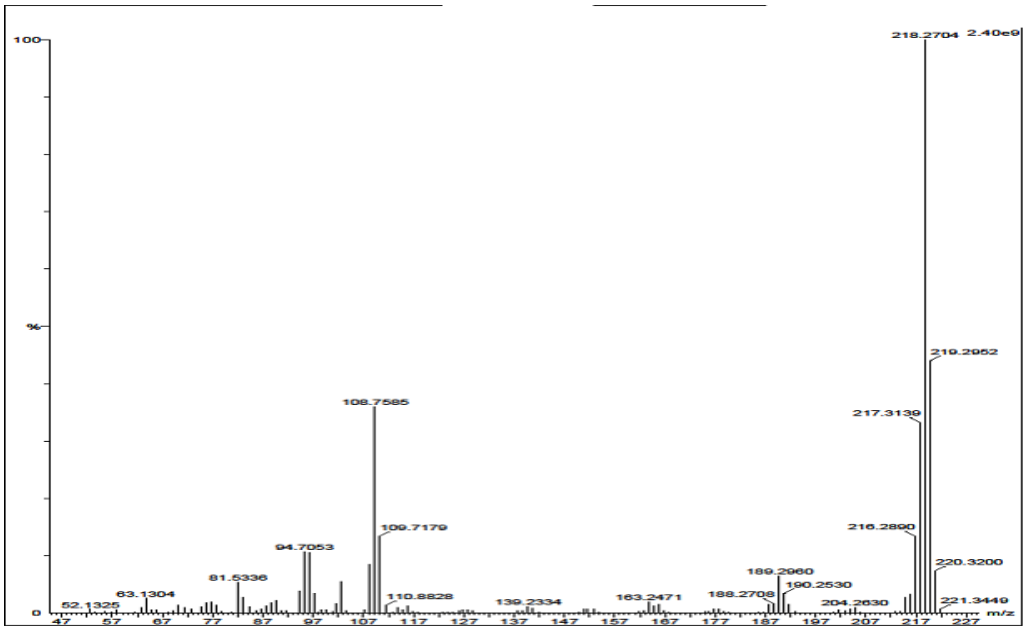
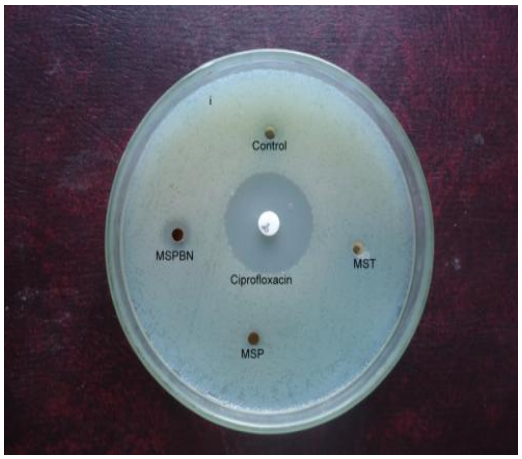


Figure 4. Mass spectra of 5,6-dihydro-11H-benzo(a)carbazole.



Pseudomonas aeruginosa

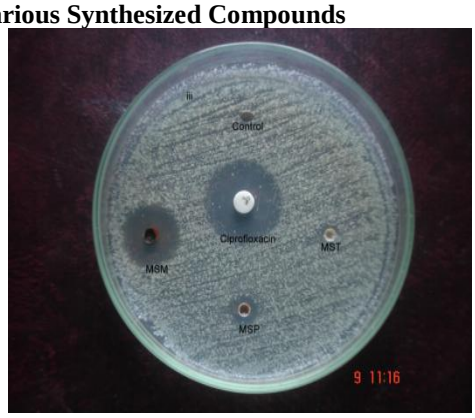
Bacillus species

Staphylococcus epidermidis

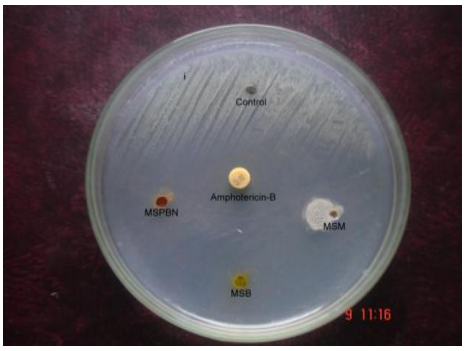
Pseudomonas aeruginosa

Antibacterial Activity Of Various Synthesized Compounds

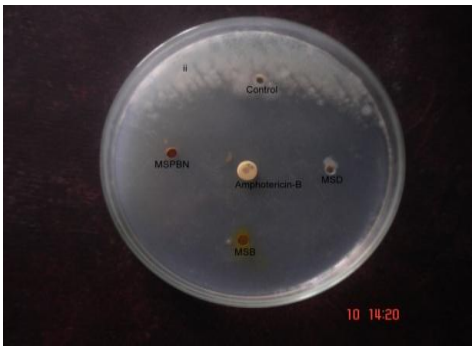
Bacillus species



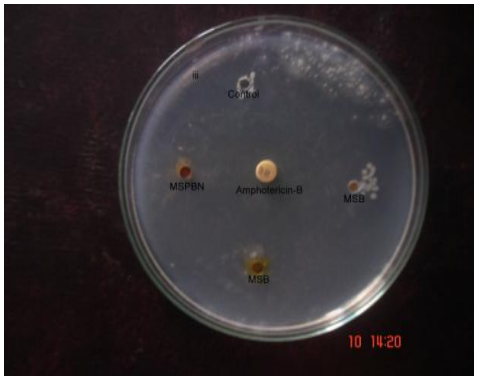
Staphylococcus epidermidis



Candida tropicalis

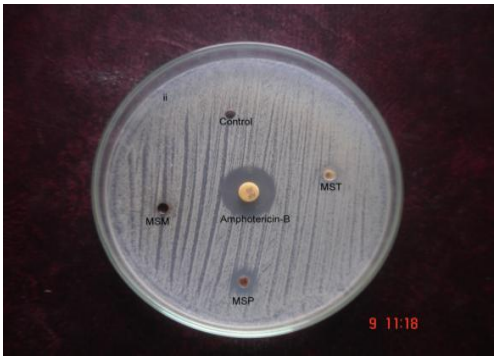


Aspergillus flavus



Aspergillus niger

Candida tropicalis



Aspergillus flavus

Aspergillus niger

Antifungal activity of various synthesized compounds.