National Conference on New Horizons in Material Science
© 2018 IJSRSET | Volume 4 | Issue 3 | Print ISSN: 2395-1990 | Online ISSN : 2394-4099
Themed Section : Engineering and Technology

Study of Antimicrobial and Antifungal Activity of the Bis-Indole Derivatives of 2-Phenyl-1-H-Indole

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ABSTRACT

The novel clay material was found to catalyze electrophilic substitution reaction of 2-phenyl-1-H-indole with a variety of aromatic aldehydes to excellent yields of bis (indolyl)methanes at room temperature. The compound 3-((4-chlorophenyl)(2-phenyl-1H-indol-3-yl)methyl)-2-phenyl-1H-indole shows more antibacterial activity towards S. aureus and E. coli than standard drug Amplicillin.

Keywords : Novel Clay, BIM, DIM, XRD, EDS, FESEM,2-phenyl-1-H-indole, substituted aromatic aldehydes, nanomaterial, E.coli, P.aeruginosa, S.aureus, S.pyogenus, C.albicans, A.niger, A.clavatus.

I. INTRODUCTION

Indole derivatives are one of the most promising heterocyclic moieties, which have active sites in treating various diseases. Numerous reports were published on indole fragment and its derivatives, capable to exhibit antimicrobial activities [1].Infectious diseases caused by microbes such as bacteria and fungi are one of the leading causes of morbidity and mortality and The major reason for the increase in microbial infections is the resistance developed by these microbial organisms, particularly gram-positive bacteria s. aureus towards existing antimicrobial drugs. Therefore development of alternative new more effective antimicrobial agents with new modes of action and a broad spectrum of activities is a one of the major challenges in drug discovery. Molecular hybridization involves combining two or more heterocyclic rings in a single molecule wherein combining units are derived from known bioactive molecules [2].The emergence and spread of antimicrobial resistance has become one of the most serious public health concerns across the world.

Antimicrobial resistance refers to micro-organism that has developed the ability to inactivate, exclude or block the inhibitory or lethal mechanism of the antimicrobial agents. Electron-rich nitrogen heterocycles play an important role in diverse medicinal chemistry [3].The indolering system are ubiquitous heterocycles that represents an important structural component in many pharmacologically active compounds, agro chemistry, dyes, material science as well as in synthetic chemistry [4].Derivatives of 2-phenyl-1-H-indole were found to inhibit the growth of human breast cancer cells by different mechanisms depending on the type and position of the substituents [5]. Substituted methane with two units of indole is commonly known as bis (indolyl) methane (BIM) or diindolylmethane (DIM) is present in various natural products possessinganticancer activity. DIMs induce apoptosis in many cancer cells by signaling various proapoptotic genes and proteins [6].

Bis (indolyl) methane (BIMs) isolated from marines or terrestrial matrices exhibit a wide range of pharmacological activities against various tumor cells. Naturally occurring BIMs such as vibrindoles are useful in the treatment of fibromyalgia, chronic fatigue and irritable bowel syndrome [7]. Indole and its derivatives have wide range of applications in biological and medicinal activities [8].Bis indole derivatives not only increase the natural metabolism of hormones in the

body and also used as anticancer drug [9].Such as anti-bacterial antitumor. Bis(indolyl) methane are members of promising new drug class these are diarylamidine derivatives that target DNA synthesis, providing a broad-spectrum antibacterial activity [10].For the synthesis of bis indole from indole different catalyst are reported such asI_2, PCl_5, PPA/SiO_2, silica sulphuric acid, Lewis acid, protic acid [11].However, many of procedures have significant drawbacks such as required stoichiometric amount of catalyst, long reaction time, expensive catalyst, low yield and use of environmentally toxic reagents. But in the present work, we replaced this catalyst by low cost cheaply available clay.

II. MATERIAL AND METHODS

2.1. Chemistry

All chemicals were purchased from major chemical suppliers of high or highest purity grade and used without further purification. As a part of our study of Chemistry indole [Biological active moiety] we have synthesized bis indole derivatives by using Novel Clay catalyst. TLC is run in N- hexane and ethyl acetate in required amount.FT-IR is recorded in KBr, HNMR in $CDCl_3$ from Central instrumentation facility (CIF), Savitribai Phule Pune University. X-Ray Powder diffraction (XRD) is recorded from department of Physics. Energy Dispersive X-Ray Spectroscopy (EDS) and Field Emission Scanning Electron Microscope (FESEM) by using instrument Nova Nano SEM 450 UOP were recorded from (CIF),Savitribai Phule Pune University, Maharashtra.

All the synthesized drugs were used for antibacterial test procedures, All necessary controls like drug control, vehicle control, agar control, organism control, known antibacterial drugs control, all MTCC cultures were tested against above mentioned known and unknown drugs, muellerhinton broth was used as nutrient medium to grow and dilute the drug suspension for the test bacteria, inoculum size for test strain was adjust to 10^8cfu [Colony Forming Unit] per milliliter by comparing the turbidity, Following common standard strains were used for screening of antibacterial and antifungal activities: The strains were procured from Institute of Microbial Technology, Chandigarh.

E.coli	P.aeruginosa	S.aureus	S.pyogenus	C.albicans	A.niger	A.clavatus
MTCC 443	MTCC 1688	MTCC 96	MTCC 442	MTCC 227	MTCC 282	MTCC 1323

DMSO was used as diluents / vehicle to get desired concentration of drugs to test upon Standard bacterial strains.Minimal Inhibition Concentration [mic] the main advantage of the 'Broth Dilution Method'for MIC determination lies in the fact that it can readily be converted to determine the MIC as well.Serial dilutions were prepared in primary and secondary screening.The control tube containing no antibiotic is immediately sub cultured [before inoculation] by spreading a loopful evenly over a quarter of p[late of medium suitable for the growth of the test organism and put for incubation at 37 ^{0}C Overnight. The tubes are then incubated overnight.The MIC of the control organism is read to check the accuracy of the drug concentrations. The lowest concentration inhibiting growth of the organism is recorded as the MIC. The amount of growth from the control tube before incubation [which represents the original inoculum] is compared.

Methods used for primary and secondary screening, each synthesized drug were diluted obtaining 2000 microgram /ml concentration, as a stock solution.In primary screening 1000 micro/ml, 500 micro/ml, and 250 micro/ml concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. Secondary screen the drugs found active in primary screening were similarly diluted to obtain 200 micro/ml 100 micro/ml, 50 micro/ml, 25 micro/ml, 12.5 micro/ml, 6.250 micro/ml, and concentrations. Reading result the highest dilution showing at least 99 % inhibition zone is taken as MIC.The result of this is much affected by the size of the inoculum. The test mixture should contain 10^8 organism/ml.

2.2. Preparation of catalyst

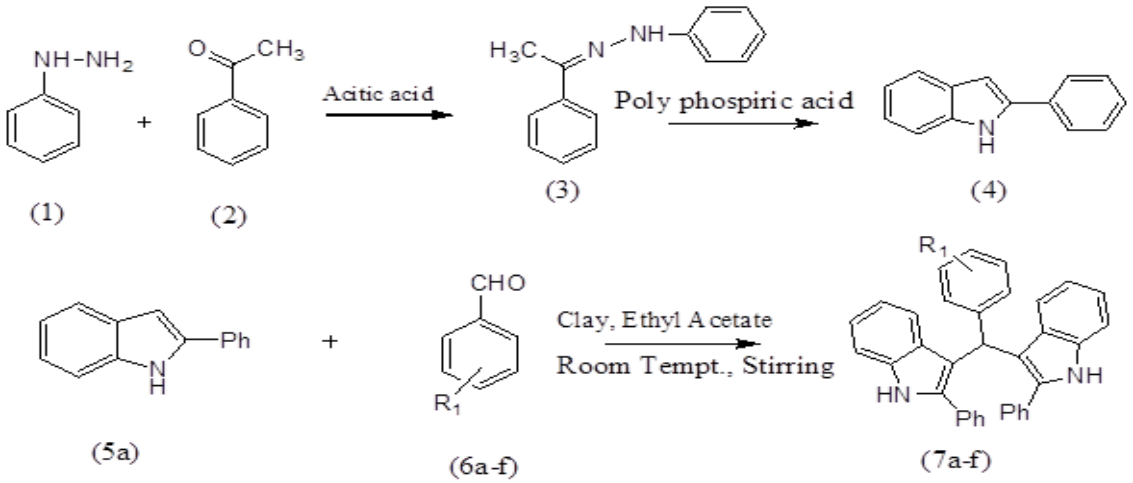
The activation of clay catalyst was done as per the procedure explained in our previous report [8, 15, and 16]. The clay was obtained from the field of Bashir Farm (Jatadevala) Tq Pathardi& Dist. Ahmednagar, Maharashtra, India.

2.3. Synthesis of 2-phenyl-1-H-Indole

Acetophenone (1mole) and phenyl hydrazine (1mole) is taken in beaker, two to three drop of acetic acid is added to mixture, stirred well and heat reaction mixture in water bath for five minutes solid hydrazone product is separated recrystallize with ethanol. Take 5 ml poly phosphoric acid in beaker and add hydrazone prepared in last stage stir well heat this mixture in water bath for five minutes the then pour this reaction mixture in to ice cold water solid product is separated out filter it and dry and recrystallize with ethanol.

2.4. The synthesis of bis-indole derivatives.

Themixture of aldehydeone mole,2-Phenyl-1-H-indole twomoles and catalyst 0.10 mg in ethyl acetate is grinded in mortar and pestle for specific period. The reaction was monitored by TLC.Reactions checked by TLC then add 10ml dichloromethane then reaction mixture was filtered. Catalyst is separated by filtration. This catalyst was reused. Then some amount of n-hexane is added in solvent.This mixture was kept in deep freezer pure crystals are separated. We have synthesized five bis-indole derivative syntheses by this method. The general scheme is given below we also compare this reaction with stone powder as catalyst but the reactive gives moderate yield and require longer duration of time.



III. RESULT

Table 1

Sr. no.	Compound name	Antibacterial Activity				Antifungal Activity	
		E.coli	P.aeruginoa	S.aurus	S.pyogenus	Calibicans	A.niger
01	3-((4-nitrophenyl)(2-phenyl-1H-indol-3-yl) methyl)-2-phenyl-1H-indole.	125	62.5	125	125	≥1000	500
02	3-((4-chlorophenyl)(2-phenyl-1H-indol-3-yl) methyl)-2-phenyl-1H-indole.	62.5	100	100	200	500	500
06	Gentamycin	0.05	1	0.25	0.5	-	-
07	Ampicillin	100	-	250	100	-	-
08	Chloramphenicol	50	50	50	50	-	-
09	Ciprofloxin	25	25	50	50	-	-
10	Norfloxacin	10	10	10	10	-	-
11	Nystatin	-	-	-	-	100	100
12	Greseofulvin	-	-	-	-	500	100

IV. DISCUSSION

3-((4-nitrophenyl)(2-phenyl-1H-indol-3-yl)methyl)-2-phenyl-1H-indoleshows antibacterial activity for bacteria E.coli at 125 mg/ml, P.aeruginosa at 62.5 mg/ml, S.aureus 125 mg/ml and S.pyogenus 125 mg/ml. Standard drug Amplicillin for E.coli 100 mg/ml, S.aureus 250 mg/ml and S.pyogenus 100 mg/ml. this conclude that this compound shows two times better reactivity than standard drug Amplicillin for bacteria S. aureus and less reactivity than Amplicillin for bacteria E. coli, P. aeruginosa and S. pyogenus. Gentamycin for E.coli 0.05 mg/ml, P.aeruginosa 1 mg/ml, S.aureus 0.25 mg/ml and S.pyogenus 0.5 mg/ml Standard drug Chloramphenicol for E.coli 50 mg/ml, P.aeruginosa 50 mg/ml, S.aureus 50 mg/ml and S.pyogenus 50 mg/ml. Standard drug Ciprofloxacin for E.coli 25 mg/ml, P.aeruginosa 25 mg/ml, S.aureus 50 mg/ml and S.pyogenus 50 mg/ml. Standard drug Norfloxacin for E.coli 10 mg/ml, P.aeruginosa 10 mg/ml, S.aureus 10 mg/ml and S.pyogenus 10 mg/ml. Hence the compound first shows less reactivity than all standard drugs.Antifungal activity of compound first for fungus C.albicans is 500, A. niger is 500 and minimal fungicidal concentration for standard drug Nystatin 100 mg/ml, A.niger 100 mg/ml, A.clavatus 100 mg/ml. Standard drug Nystatin 500 mg/ml, A.niger 100 mg/ml, A.clavatus 100 mg/ml.

3-((4-chlorophenyl)(2-phenyl-1H-indol-3-yl)methyl)-2-phenyl-1H-indole shows antibacterial activity for bacteria E.coli at 62.5 mg/ml, P.aeruginosa at 100 mg/ml, S.aureus 100 mg/ml and S.pyogenus 200 mg/ml. Standard drug Gentamycin for E.coli 0.05 mg/ml, P.aeruginosa 1 mg/ml, S.aureus 0.25 mg/ml and S.pyogenus 0.5 mg/ml. Standard drug Amplicillin for E.coli 100 mg/ml, S.aureus 250 mg/ml and S.pyogenus 100 mg/ml. Standard drug Chloramphenicol for E.coli 50 mg/ml, P.aeruginosa 50 mg/ml, S.aureus 50 mg/ml and S.pyogenus 50 mg/ml. Standard drug Ciprofloxacin for E.coli 25 mg/ml, P.aeruginosa 25 mg/ml, S.aureus 50 mg/ml and S.pyogenus 50 mg/ml. Standard drug Norfloxacin for E.coli 10 mg/ml, P.aeruginosa 10 mg/ml, S.aureus 10 mg/ml and S.pyogenus 10 mg/ml. Hence the compound first shows less reactivity than all standard drugs.Antifungal activity of compound first for fungus C.albicans is 500, A. niger is 500 and minimal fungicidal concentration for standard drug Nystatin 100 mg/ml, A.niger 100 mg/ml, A.clavatus 100 mg/ml. Standard drug Nystatin 500 mg/ml, A.niger 100 mg/ml, A.clavatus 100 mg/ml. according this it observed that greseofulvin and this compound shows that similar antifungal activity fungi C.Albicans.

V. CONCLUSION.

Ecofriendly synthesis of bisindole by using novel clay catalyst with substituted aldehyde and 2-phenyl-1-H-indole is reported at room temperature, this procedure has short reaction time and clean and good yield. Compound3-((4-nitrophenyl)(2-phenyl-1H-indol-3-yl)methyl)-2-phenyl-1H-indole and 3-((4-chlorophenyl)(2-phenyl-1H-indol-3-yl)methyl)-2-phenyl-1H-indoleshows more antibacterial activity towards S. aureus than standard drug Amplicillin 3-((4-chlorophenyl)(2-phenyl-1H-indol-3-yl)methyl)-2-phenyl-1H-indoleshows more antibacterial activity towards E. coli than standard drug Amplicillin.

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