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Research Article

EVALUATION OF ANTIBACTERIAL ACTIVITY OF HUMAN BACTERIAL PATHOGENS WITH NOVEL SYNTHETIC OXINDOLE DERIVATIVES

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Abstract

Derivatives of Indole-type compounds constitute an important class of compounds for new drug development in order to discover an effective compound against multi-drug-resistant microbial infections. Experimental studies have shown the antimicrobial analysis of oxindole derivative compounds with clinical bacterial pathogens of humans like *Staphylococcus aureus, Enterococcus faecalis, Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa, Proteus mirabilis, Salmonella typhimurium, Salmonella typhi, Salmonella paratyphi 'A', Shigella sonnei* and *Vibrio cholera*. The current study investigates the MICs of six Oxindole derivatives namely 3-hydroxy-3-naphthyl-oxindole, 1-N-allyl-3,3-P-dimethoxy- diphenyl-oxindole, 1-N-allyl-3,3- diphenyl-oxindole, 1-N-allyl-3,3-P-dimethyl diphenyl-oxindole, 1-N-benzyl-3,3-dinaphthyl- oxindole and 1-N-allyl-3,3-dinaphthyl- oxindole compounds with the eleven bacterial pathogens. The MIC's of six different oxindole compounds are compared with standard antibiotic like Ampicillin dissolved in various concentrations of 100, 150 & 200 µg/ml in Dimethyl Sulfoxide (DMSO). The Oxindole derivative compounds are found to show potent activity against most of the pathogens tested. Most of the derivatives were especially effective against *P.aeruginosa, S.typhimurium, E.feacalis* and *Klebsiella pneumonia*. Hence, further research on indole compounds and their derivatives could be studied out for better understanding of their antimicrobial activity using laboratory and computational tools.

Keywords: Oxindole, Minimum Inhibitory Concentrations (MICs), DMSO, Ampicillin.

Introduction

An antibiotic is a chemotherapeutic agent that inhibits or destroys the growth of microorganisms such as bacteria, fungi or protozoans. Due to resistance developed by various microorganisms towards the antibiotic produced against

the microorganisms, many synthetic chemicals have been developed to overcome this phenomenon. Some of the synthetic drugs (or) chemotherapeutic agents widely used were derivatives of Indole [1], Ferrocene [2], Dipeptides [3], Ginsensosides [4], Pyrrolidine [5], Pyridine [6] and Quinoline [7,8] compounds. The synthetic compounds used in the present study are Oxindole substituted derivatives. These derivative compounds have potent activities against both gram-positive and gram-negative bacteria. Resistance is a problem in the community in health care, where transmission of bacteria is greatly amplified. Because multiple drug resistance is a growing problem, physicians are now confronted with infections for which there is no effective therapy. As result, structurally novel antibacterials like Oxindole substituted derivatives with a new mode of action have become important in the treatment of bacterial infections.

Oxindoles are endogenous aromatic organic compounds that are found in the tissues and body fluids of mammals, and in the natural products of some plants. They are aromatic heterocyclic organic compounds with a bicyclic structure. An oxindole molecule consists of a six membered benzene ring that is fused to a five-membered ring containing nitrogen. Oxindole structure is based on the indoline structure but where a carbonyl is situated at the 2-position of the 5 membered ring [9].

Oxindole derivatives have a wide range of biological applications which include antiviral, antifungal, antibacterial, antiproliferative, anticancer, anti-inflammatory, antihypertensive and the anticonvulsant activities [10, 11]. The oxindole oxazolidinone derivative is reported to act as an antibacterial by inhibiting bacterial protein synthesis, and is used for treatment of many serious infections that are caused by verterinary and human pathogens and multiple resistant strains of bacteria [12]. The present study was conducted for studying the biochemical characteristics and antibacterial activity of commonly identified eleven different pathogens with six synthesized oxindole derivatives [13, 14].

The antibacterial activities of Oxindole derivative compounds with eleven different gram-positive and gram-negative species of bacteria are determined by the Minimum Inhibitory Concentration (MIC) values, which can be determined by a number of standard test procedures. The tube dilution method and agar dilution method procedures are used for the preparation. Serial dilutions are prepared from Oxindole substituted derivatives in bacterial growth media. The test organisms are then added to the dilutions of the products, incubated, and scored for growth and so the procedure incorporates the content and intent of the American Society for Microbiology (ASM) recommended

methodology [15].

Materials and Methods

Collection of Standard Cultures:

The bacterial strains used in the study were *Staphylococcus aureus* (ATCC 25923), *Enterococcus faecalis* (ATCC 29212), *Escherichia coli* (MTCC 1687), *Klebsiella pneumonia* (ATCC 29665), *Pseudomonas aeruginosa* (ATCC 29212), *Proteus mirabilis* (ATCC 6539), *Salmonella typhimurium* (MTCC 1265), *Salmonella typhi* (ATCC 7002), obtained from IMTECH, Chandigarh, ATCC, Bangalore and three clinical strains of *Salmonella paratyphi 'A'*, *Shigella sonnei* and *Vibrio cholera*, which were obtained from Department of Microbiology, Prince Shri Venkateswara Arts & Science College.

Collection of Synthetic Chemical Compounds:

The Oxindole substituted derivative compounds namely 3-hydroxy-3-naphthyl-oxindole, 1-N-allyl-3,3-P-dimethoxy- diphenyl-oxindole, 1-N-allyl-3,3- diphenyl-oxindole, 1-N-allyl-3,3-P-dimethyl diphenyl-oxindole, 1-N-benzyl-3,3-dinaphthyl- oxindole, 1-N-allyl-3,3-dinaphthyl- oxindole as shown in Figure 1-6 used for this study were obtained from Department of Organic Chemistry, University of Madras, Guindy campus, Chennai-600032, which includes

Figure-1: 3-hydroxy-3-naphthyl-oxindole.

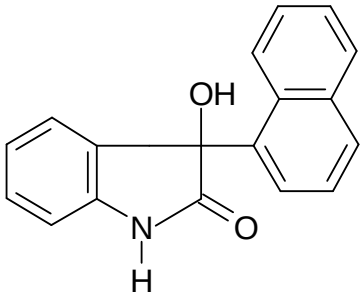


Figure-2: 1-N-allyl-3, 3-(p-dimethyoxy diphenyl-oxindole).

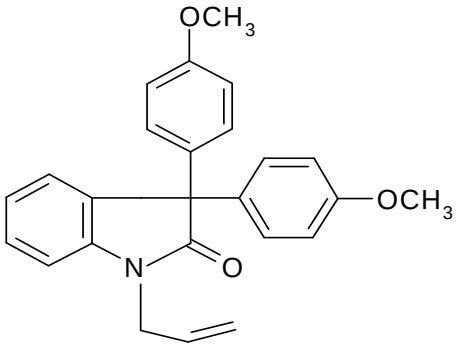


Figure-3: 1-N-allyl-3, 3-diphenyl-oxindole.

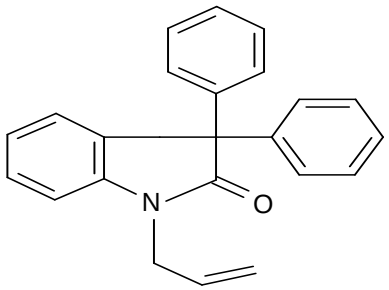


Figure-4: 1-N-allyl-3, 3-(p-dimethyl diphenyl)-oxindole.

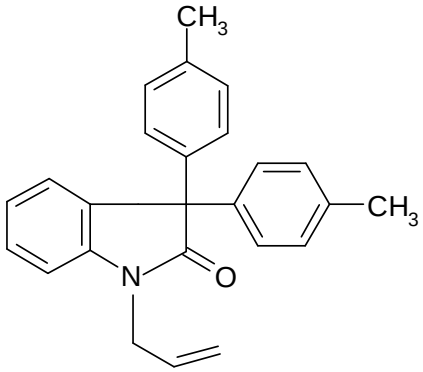


Figure-5: 1-N-Benzyl-3, 3-(dinaphthyl)-oxindole.

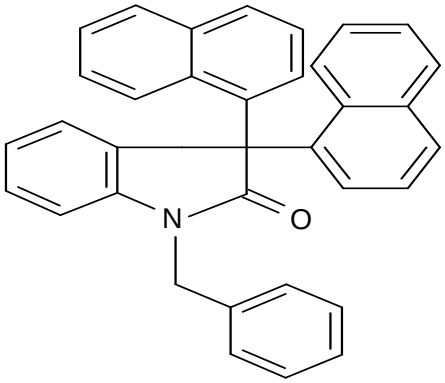
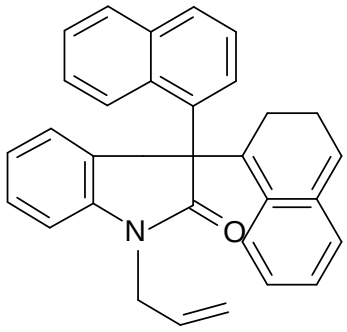


Figure-6: 1-N-allyl-3, 3-(dinaphthyl)-oxindole.



Characterization of bacterial pathogens using biochemical tests:

The clinical, MTCC and ATCC cultures of bacterial pathogens were subjected to various microbial identification tests like gram staining, motility, oxidase, catalase, and for biochemical tests like indole, methyl red, Voges Prokauer, citrate utilization, and coagulase tests.

Preparation of McFarland Standard (0.5) and Inoculum [16]:

Solution A and solution B were prepared by dissolving 1.175 g of $BaCl_2.2H_20$ and 1 ml of H_2SO_4 in 100 ml of distilled water. 0.5 ml of solution A was added to 99.5 ml of solution B and mixed well. It was mixed well with magnetic stirrer and then distributed in test tubes with a screw cap of the same size as those containing the bacterial culture, the turbidity of which must be evaluated. The standard was stored in ambient temperature in the dark. The cap was closed tightly to avoid evaporation or flame sealed. It was agitated vigorously in a vortex before using it. The ATCC strain of bacterial pathogen culture was inoculated into nutrient broth and incubated at 37°C for 24 hours and adjusted according to McFarland standard 0.5 that gives approximately 10^5 cells /ml.

Determination of Antibacterial Activity [17]:

The antibacterial assay of synthetic chemical compounds was carried out by well diffusion method. 20ml of nutrient agar medium for bacterial strains were poured into the sterile petridishes and allowed to set. A sterile cotton swab dipped in 24 hours bacterial cultures and was inoculated in the petriplates containing sterile Nutrient Agar. Wells were made in the solidified plate by using a sterile cork borer 10mm in diameter. After inoculating, the compounds were dissolved separately with the Dimethyl sulfoxide (DMSO) solvent and poured into the wells with varying concentrations ranging from 100µg/ml, 150µg/ml and 200µg/ml using a micropipette. The plates were left over for 24 hours at 37°C. The antibiotic Ampicillin was used as a standard for comparative study for bacterial strains. After 24 hours of incubation, the zone of inhibition was observed and measured.

The percentage of inhibition was calculated by the formula,

% Inhibition = (Diameter of the inhibition zone in mm / Diameter of the standard in mm) X 100.

Results and Discussion

The bacterial cultures were characterized based on gram staining, motility, oxidase, catalase and bio chemical tests (using indole, methyl red, vogues prokauer, citrate and coagulase) [18] and is listed in Table1 below.

S.No	Tests	*Staphylococcus aureus*	*Enterococcus faecalis*	*Klebsiella pneumonia*	*Escherichia coli*	*Proteus mirabilis*	*Pseudomonas aeruginosa*	*Salmonella typhi*	*Shigella sonnei*	*Vibrio cholera*	*Salmonella typhimurium*	*Salmonella paratyphi 'A'*
1	Gram staining	+ve cocci	+ve cocci	-ve rod	-ve rod	-ve rod	-ve rod	-ve rod	-ve rod	-ve rod	-ve rod	-ve rod
2	Motility	-	-	-	+	+	+	+	-	+	+	+
3	Oxidase	-	-	-	-	-	+	-	-	+	-	-
4	Catalase	+	-	+	+	+	+	+	+	+	+	+
5	Indole	-	-	-	+	-	-	-	-	+	-	-
6	Methyl Red	+	-	-	+	+	-	+	+	-	+	+
7	Voges Prokauer	+	+	+	-	-	-	-	-	-	-	-
8	Citrate utilization	+	-	+	-	+	+	-	-	+	-	+
9	Coagulase	+	-	-	-	-	-	-	-	-	-	-

The antibacterial activity of the synthetic oxindole compounds were determined against eleven bacterial pathogens showing zone of inhibition for the three different DMSO concentrations [19] of 100 µg/ml, 150 µg/ml and 200 µg/ml ($P<0.05$, two tailored student's t-test). Ampicillin was used as the standard antibiotic and the zone of inhibition for the bacterial cultures at three concentrations were tabulated in Table 2.

Table-2: Antibacterial activity of standard antibiotic–Ampicillin.

S.No	**Human Pathogens**	**Zone of inhibition {Mean values and Standard Error (±)}**		
		100µg/ml	**150µg/ml**	**200µg/ml**
		mm	**Mm**	**mm**
1	*Staphylococcus aureus*	35±2	35±1	35±2
2	*Enterococcus faecelis*	18±1	20±1	20±1
3	*Escherichia coli*	24±2	30±2	40±2
4	*Klebsiella pneumonia*	12±2	12±2	15±2

5	*Pseudomonas aeruginosa*	15±1	15±2	22±1
6	*Proteus mirabilis*	20±3	30±1	30±2
7	*Salmonella typhi*	28±1	28±2	28±2
8	*Salmonella paratyphi 'A'*	30±1	30±2	30±3
9	*Salmonella typhimurium*	20±2	20±2	20±2
10	*Shigella sonnei*	22±2	22±3	22±3
11	*Vibrio cholera*	35±1	35±2	35±2

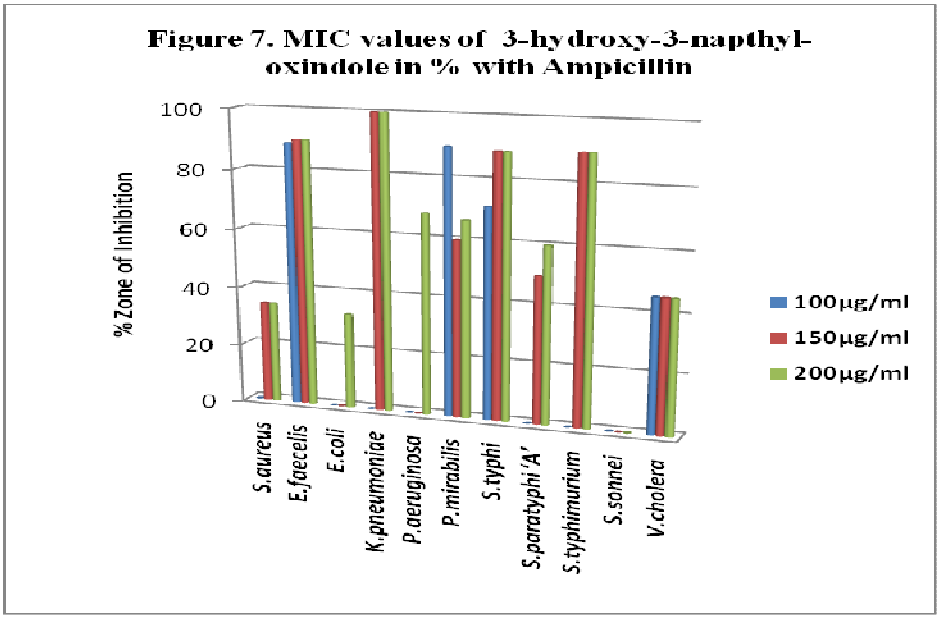
The experimental study has proved a measurable invitro antimicrobial activity like a standard antibiotic-Ampicillin which is generally targeted against human pathogens ($P<0.05$, two tailored student's t-test). The bacterial cultures used here are considered to be common pathogens [20].

3-hydroxy-3-naphthyl-oxindole showed higher activity of 90-100% or more against *E.faecalis, S.typhimurium* and *Klebsiella Pneumoniae* and a moderate activity of about 40-90% was detected against *Pseudomonas aeruginosa, Proteus mirabilis, V. cholera*, *S.typhi* and *S.aureus* showed activity of less than 40% whereas *Shigella sonnei* was found to be highly resistant to 3-hydroxy-3-naphthyl-oxindole compound showing no activity as shown in Table-3 and Figure-7.

Table-3: Antibacterial activity of 3-hydroxy-3-naphthyl-oxindole.

S.No	**Human Pathogens**	**Zone of inhibition {Mean values and Standard Error (±)}**		
		100µg/ml	**150µg/ml**	**200µg/ml**
		mm	**mm**	**mm**
1	*Staphylococcus aureus*	-	12±1	12±2
2	*Enterococcus faecelis*	16±1	18±1	18±2
3	*Escherichia coli*	-	-	13±2
4	*Klebsiella pneumoniae*	-	12±1	15±1
5	*Pseudomonas aeruginosa*	-	-	15±2

6	*Proteus mirabilis*	18±1	18±1	20±1
7	*Salmonella typhi*	20±1	25±2	25±2
8	*Salmonella paratyphi 'A'*	-	15±1	18±2
9	*Salmonella typhimurium*	-	18±1	18±2
10	*Shigella sonnei*	-	-	-
11	*Vibrio cholera*	16±1	16±2	16±2

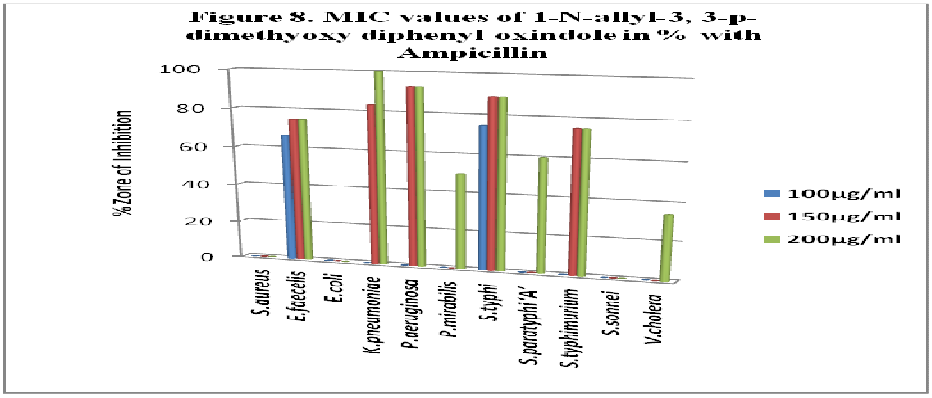


1-N-allyl-3, 3-(p-dimethyoxy diphenyl-oxindole) showed higher activity of 90-100% or more against *P.aeruginosa, S.typhi* and *Klebsiella pneumonia* and a moderate activity of 50-75% was detected against *Proteus mirabilis, E.faecalis, S.typhimurium* and *S.paratyphi'A'. V.cholerae* showed activity of less than 40% whereas *Shigella sonnei, E.coli* and *S.aureus* was found to be highly resistant to the 1-N-allyl-3, 3-(p-dimethyoxy diphenyl-oxindole) compound showing no activity as shown in Table-4 and Figure-8.

Table-4: Antibacterial activity of 1-N-allyl-3, 3-(p-dimethyoxy diphenyl-oxindole).

S.No	Human Pathogens	Zone of inhibition {Mean values and Standard Error (±)}		
		100µg/ml	150µg/ml	200µg/ml
		mm	mm	mm

1	*Staphylococcus aureus*	-	-	-
2	*Enterococcus faecelis*	12±1	15±2	15±3
3	*Escherichia coli*	-	-	-
4	*Klebsiella pneumoniae*	-	10±1	15±1
5	*Pseudomonas aeruginosa*	-	14±1	14±1
6	*Proteus mirabilis*	-	-	15±2
7	*Salmonella typhi*	21±2	25±1	25±2
8	*Salmonella paratyphi 'A'*	-	-	18±1
9	*Salmonella typhimurium*	-	15±2	15±2
10	*Shigella sonnei*	-	-	-
11	*Vibrio cholera*	-	-	12±1

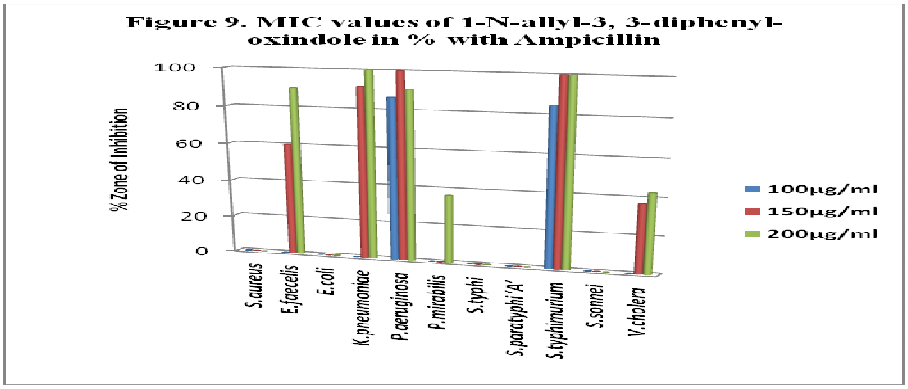


1-N-allyl-3, 3-diphenyl-oxindole showed higher activity of 80-100% against *P.aeruginosa, S.typhimurium, E.faecalis* and *Klebsiella pneumonia* whereas moderate activity of about less than 40% was detected against *Proteus mirabilis* and *V.cholerae. S.paratyphi'A', Shigella sonnei, E.coli, S.typhi* and *S.aureus* was found to be highly resistant to 1-N-allyl-3, 3-diphenyl-oxindole compound showing no activity as shown in Table 5 and Figure 9.

Table-5: Antibacterial activity of 1-N-allyl-3, 3-diphenyl-oxindole.

S.No	**Human Pathogens**	**Zone of inhibition {Mean values and Standard Error (±)}**		
		100µg/ml	**150µg/ml**	**200µg/ml**
		mm	**mm**	**mm**
1	*Staphylococcus aureus*	-	-	-

2	*Enterococcus faecelis*	-	12±2	18
3	*Escherichia coli*	-	-	-
4	*Klebsiella pneumoniae*	-	11±1	15±1
5	*Pseudomonas aeruginosa*	13±2	15±1	20±2
6	*Proteus mirabilis*	-	-	11±3
7	*Salmonella typhi*	-	-	-
8	*Salmonella paratyphi 'A'*	-	-	-
9	*Salmonella typhimurium*	17±1	20±1	20±1
10	*Shigella sonnei*	-	-	-
11	*Vibrio cholera*	-	13±3	15±2

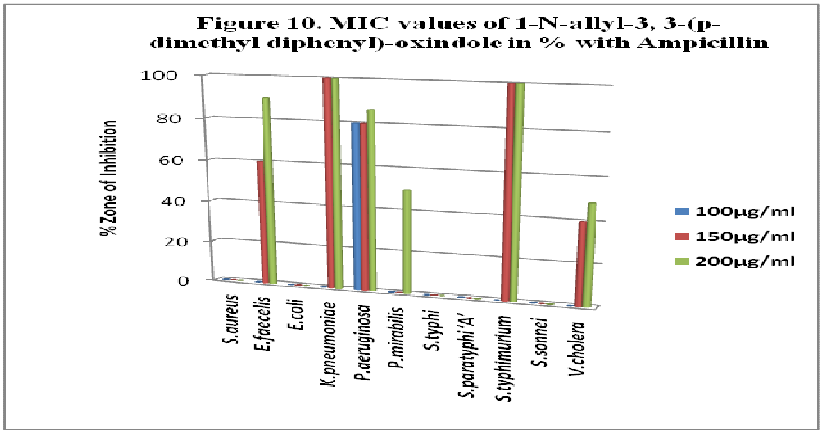


1-N-allyl-3, 3-(p-dimethyl diphenyl)-oxindole showed higher activity of 90-100% against *E.faecalis, S.typhimurium* and *Klebsiella pneumonia* whereas moderate activity of about 40-50% was detected against *Proteus mirabilis* and *V.cholerae. S.paratyphi'A', Shigella sonnei, E.coli, S.typhi* and *S.aureus* was found to be highly resistant to the 1-N-allyl-3, 3-(p-dimethyl diphenyl)-oxindole compound showing no activity as shown in Table 6 and Figure 10.

Table-6: Antibacterial activity of 1-N-allyl-3, 3-(p-dimethyl diphenyl)-oxindole.

S.No	**Human Pathogens**	**Zone of inhibition {Mean values and Standard Error (±)}**		
		100µg/ml	**150µg/ml**	**200µg/ml**
		mm	**mm**	**mm**
1	*Staphylococcus aureus*	-	-	-
2	*Enterococcus faecelis*	-	12±1	18±2
3	*Escherichia coli*	-	-	-

4	*Klebsiella pneumoniae*	-	12±1	15±1
5	*Pseudomonas aeruginosa*	12±1	12±2	19±2
6	*Proteus mirabilis*	-	-	15±3
7	*Salmonella typhi*	-	-	-
8	*Salmonella paratyphi 'A'*	-	-	-
9	*Salmonella typhimurium*	-	20±1	20±1
10	*Shigella sonnei*	-	-	-
11	*Vibrio cholera*	-	14±2	17±3

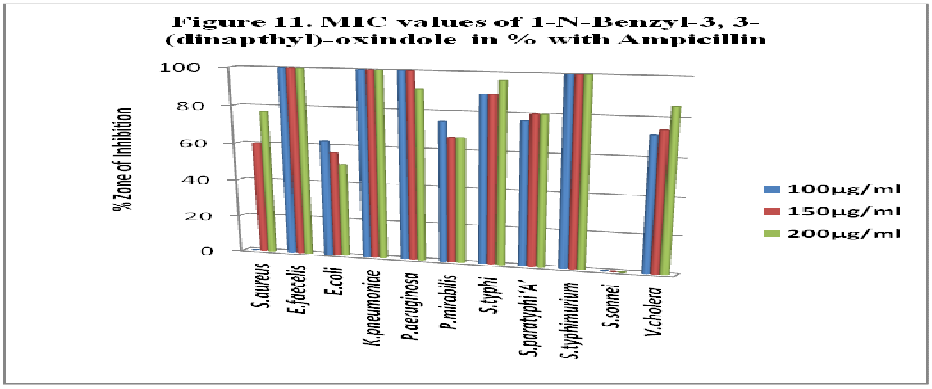


1-N-Benzyl-3, 3-(dinaphthyl)-oxindole showed higher activity of 90-100% against *P.aeruginosa, S.typhimurium, E.feacalis* and *Klebsiella pneumonia* whereas a moderate activity of about 50-80% was detected against *Proteus mirabilis, V. cholera, S.paratyphi'A', E.coli,* and *S.aureus*. *Shigella sonnei* was found to be highly resistant to 1-N-Benzyl-3, 3-(dinaphthyl)-oxindole compound showing no activity as shown in Table 7 and Figure 11.

Table-7: Antibacterial activity of 1-N-Benzyl-3, 3-dinaphthyl-oxindole.

S.No	**Human Pathogens**	**Zone of inhibition {Mean values and Standard Error (±)}**		
		100µg/ml	**150µg/ml**	**200µg/ml**
		mm	**mm**	**mm**
1	*Staphylococcus aureus*	-	21±2	27±2
2	*Enterococcus faecelis*	18±1	20±1	20±1
3	*Escherichia coli*	15±3	17±2	20±1

4	*Klebsiella pneumoniae*	12±1	12±2	15±2
5	*Pseudomonas aeruginosa*	15±1	15±1	20±2
6	*Proteus mirabilis*	15±1	20±2	20±2
7	*Salmonella typhi*	25±1	25±1	27±1
8	*Salmonella paratyphi 'A'*	23±2	24±2	24±2
9	*Salmonella typhimurium*	20±1	20±1	20±1
10	*Shigella sonnei*	-	-	-
11	*Vibrio cholera*	25±2	26±2	30±2

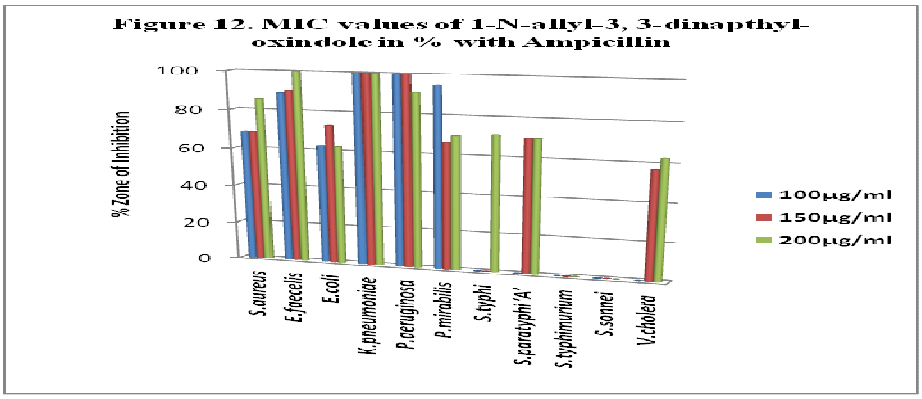


1-N-allyl-3, 3-(dinaphthyl)-oxindole showed higher activity of 90-100% against *P.aeruginosa, E.faecalis* and *Klebsiella pneumonia* whereas moderate activity of about 50-80% was detected against *Proteus mirabilis, V.cholerae, S.typhi, S.paratyphi'A', E.coli* and *S.aureus. Shigella sonnei* and *S.typhimurium* was found to be highly resistant to 1-N-allyl-3, 3-(dinaphthyl)-oxindole compound showing no activity as shown in Table 8 and Figure 12.

Table-8: Antibacterial activity of 1-N-allyl-3, 3-dinaphthyl-oxindole.

S.No	**Human Pathogens**	**Zone of inhibition {Mean values and Standard Error (±)}**		
		100µg/ml	**150µg/ml**	**200µg/ml**
		mm	**mm**	**mm**
1	*Staphylococcus aureus*	24±2	24±2	30±2
2	*Enterococcus faecelis*	16±1	18±2	20±1
3	*Escherichia coli*	15±2	22±1	25±2
4	*Klebsiella pneumoniae*	12±1	12±1	15±1

5	*Pseudomonas aeruginosa*	15±1	15±1	20±1
6	*Proteus mirabilis*	19±2	20±1	21±3
7	*Salmonella typhi*	-	-	20±1
8	*Salmonella paratyphi 'A'*	-	21±1	21±1
9	*Salmonella typhimurium*	-	-	-
10	*Shigella sonnei*	-	-	-
11	*Vibrio cholera*	-	20±2	22±3



Oxindole derivatives tested against most of the pathogenic bacteria by agar dilution method showed very good activity against all the tested pathogens and are considered as one of the effective antimicrobial agents [21]. Since indole and hexenal have broad spectrum of antimicrobial activity [22], their combination with polymyxins have broaden the antimicrobial spectra of therapeutic combinations.

Bis indole alkaloids were evaluated for antimicrobial activity against various bacteria and fungi, they showed significant antibacterial [23] and antifungal activity [24]. This study shows that the indole compounds when tested against various bacteria, they showed significant activity towards bacteria.

Frequent use of broad spectrum antibiotics against these pathogens might result in the development of drug resistant strains. In order to overcome this problem, pharmaceutical companies need to develop a novel class of synthetic chemical compounds. The experimental components are comparatively sensitive to all the microorganisms tested. The rate of inhibition may be due to the alterations found in the chemical structure. These indole compounds occupy a predominant place among the various classes of organic compounds for their biological properties and activities. Therefore, it can be concluded that a new class of indole compounds or derivatives can be used as an alternative drug to prevent and control the emergence of new drug resistant strains. Using the lead compounds we have

screened, we can use computational and laboratory techniques to refine the molecular structures to increase the activity of the drug and reduce its side effects.

Conclusion

The experimental study has proved a measurable invitro antimicrobial activity of oxindole substituted derivative compounds and with standard antibiotic like ampicillin is generally targeted against human pathogens. The bacterial cultures used here are considered to be common pathogens. Frequent use of broad spectrum antibiotics against these pathogens might result in the development of drug resistant strains. In order to overcome this problem, pharmaceutical companies need to develop a novel class of synthetic chemical compounds. The rate of inhibition may be due to the alterations found in the chemical structure of novel oxindole derivatives. These indole compounds occupy a predominant place among the various classes of organic compounds for their biological properties and activities. These oxindole derivatives occupied a predominant place among the various classes of organic compounds for their biological activities & drug-likeness properties.

Indole derivatives tested against most of the pathogenic bacteria by agar dilution method showed very good activity against all the tested pathogens and are considered as effective antimicrobial agents. Since indole compounds have broad spectrum of antimicrobial activity, their combination with polymyxins have broaden the antimicrobial spectra of therapeutic combinations. Bis indole alkaloids were evaluated for antimicrobial activity against various bacteria and fungi, they showed significant antibacterial activity. The present study proves the oxindole substituted derivative compounds tested against various bacteria has showed significant activity results towards human bacterial pathogens.

Therefore, it can be concluded that a new class of oxindole compounds or its derivatives can be used as an alternative drug to prevent and control the emergence of new drug resistant strains.

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