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SYNTHESIS, CHARECTERIZATION AND ANTI-MICROBIAL ACTIVITY OF SUBSTITUTED 5-(5-SULFANYL-1,3,4-OXADIAZOL-2-YL)BENZENE- 1,2,3-TRIOL DERIVATIVES

Vinod Kumar Nakra * [1], Manoj Sharma [2],

[1] Research Scholar, Bhagwant University, Ajmer (Rajasthan), India

[2] School of Studies in Pharmaceutical Sciences, Jiwaji University, Gwalior, M.P., India

ABSTRACT

A solution of propyl gallate(0.01 mol) in ethanol and hydrazine hydrate (0.01 mol) was refluxed for 4 hours. The excess solvent was distilled off under reduced pressure. The cooled residual mass was washed with distilled water. It was filtered and dried. The crude product was recrystallised from methanol to yield galloylhydrazide, Carbon disulfide (2 ml) was added drop wise to an ice cooled solution of KOH (2g) in ethanol (20 ml) containing the acid hydrazide 4 (0.02 mole), then the reaction mixture was stirred at room temperature 2h . After dilution with ethanol the solid precipitated was washed twice with ether. To the solid obtained (1 g), 10% KOH (20 ml) was added then the reaction mixture was refluxed for 4 hr, cooled, acidified with conc. HCl. The resulting solid was filtered washed with water, dried and crystallized. A mixture of (0.97g, 0.005mol) of 5-(5-sulfanyl- 1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol and (0.005mol) of different aryl or alkyl halides were refluxed in 25ml of pyridine solution for 3.5 hours. The resultant mixture was cooled and poured into crushed ice. The solid mass is thus separated out was dried and recrystallized from ethanol. Synthesized derivatives purity were checked by TLC, Melting point & characterized by FT-IR, Mass, NMR spectroscopic techniques. Synthesized derivatives were evaluated for anti-microbial activity.

Keywords: Oxadiazole, Oxadiazole derivatives, Anti-microbial activity.

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***Address for Correspondence:**

Vinod Nakra, Research Scholar, Bhagwant University, Ajmer (Rajasthan), India

INTRODUCTON:

During the 19th century, the French scientist Louis Paster and German physician demonstrated the roll of bacteria as pathogens the discovery of compound produce by bacteria and fungi have shown their the lethal effect to other bacteria led to development of antibiotics[1,2] Bacteria are free living, microscopic, unicellular organism capable of performing all the essential functions of life i.e. growth, metabolism and reproduction .They possess both deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) and lack of chlorophyll. Bacteria have been placed in a kingdom separate from the animal and plant kingdoms. Scientist use various system for classifying bacteria based on different, shapes, dependence on oxygen and by staining techniques.

Agents that inhibit bacterial cell wall synthesis:

This includes β-lactamase antibiotics, like Ampicilin and Cephalosporines and Azole derivatives. β-lactamase inhibits D-alanyl-D-alanine transpeptidase activity by acylation, forming stable esters with opened lactum ring attached to hydroxyl group of the enzymes active site.

Agents that interfere with DNA-RNA synthesis:

Quinolones, are bactericidals and they inhibit DNA gyrase synthesis,Eg. Ciprofloxacine, norfloxacine, sparfloxacine.

Sulphonamides inhibit microbial growth by inhibiting P-aminobenzoic acid (PABA) involved in folic acid synthesis.

Antimetabolites:

An antimetabolite is a chemical that inhibits the use of a metabolite, which is another chemical that is part of normal metabolism.[21] Such substances are often similar in structure to the metabolite that they interfere with, such as the antifolates that interfere with the use of folic acid.

Agents that interfere with protein synthesis:

This class includes, Tetra cyclones, which block and binds aminoacyl receptor site of tRNA, Chloramphinicol, and

Erythromycines, binds p-sites of the 50S ribosomal subunit and inhibit translation.[19]

Oxadiazoles

The 1, 2, 3-isomer is unstable and reverts to the diazoketone tautomer[3]Oxadiazoles were discovered against the schistosomiasis-causing fluke in the year 2008. It did not show any negative effects on humans. The stable oxadiazoles appear in a variety of pharmaceutical drugs including raltegravir (anti-retroviral), butalamine, fasiplon, oxolamine, and pleconaril. Tiodazosin, nosapidil, furamizole are other examples.[4]

Naturally Ocurring Oxadiazoles:

There are only few examples of natural products with oxadiazole core or a structure based on it. One among this is phidianidines A and B (Figure 1), this is a 3-substituted indole alkaloid. Phidianidines A and B have been isolated by Carbone et al. from the aeolidopisthobranchPhidiana militaris.[5]

Chemistry

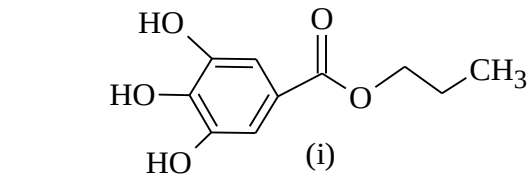
Due to the presence of a heteroatom in the ring, oxadiazole shows inductive effect and thus it is considered to be a weak base. It consists of 2 pyridine like nitrogen, due to which it exhibits conjugate diene type character. Electrophillic substitution at carbon is very difficult in this case due to less electron density which is mainly due to the presence of pyridine like nitrogen in the ring that shows electron withdrawal effect.

MATERIAL AND METHODS:

1. **SYNTHETIC PROCEDURE:**

1.1 General procedure for preparation of 5-[5-(substitutedsufanyl)-1,3,4-oxadiazole-2-yl]benzene-1,2,3-triol (iva-j)

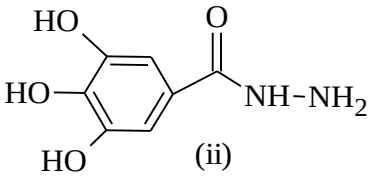
A mixture of (0.97g, 0.005mol) of 5-(5-sulfanyl- 1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol and (0.005mol) of different aryl or alkyl halides were refluxed in 25ml of pyridine solution for 3.5 hours. The resultant mixture was cooled and poured into crushed ice. The solid mass is thus separated out was dried and recrystallized from ethanol.



(i)

propyl 3,4,5-trihydroxybenzoate /(propyl gallate)

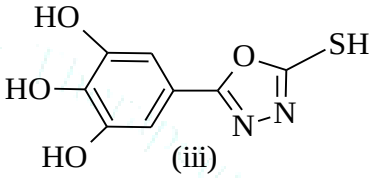
$NH_2NH_2.H_2O$ | EtOH, Reflux, 4 hr.



(ii)

3,4,5-trihydroxybenzohydrazide/(galloyl hydrazide)

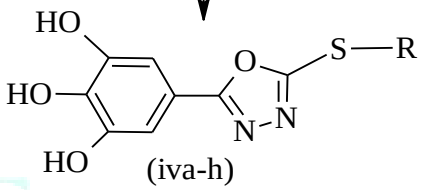
KOH/CS_2 | EtOH, Reflux, 4 hr.



(iii)

5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

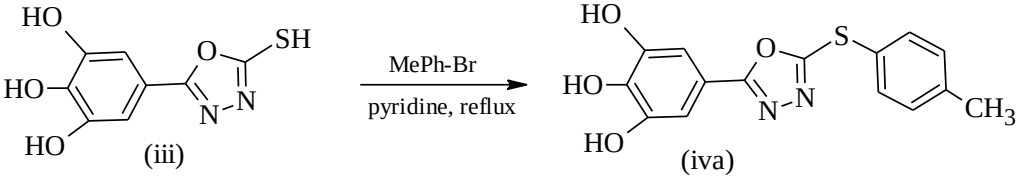
R-Br



(iva-h)

Where **R= iva**=Ar-CH_3**ivb**=Ar-OCH_3**ivc**=Ar-OH **ivd**=Ar-NO_2**ive**=Ar-C_2H_5 **ivf**=CH_3**ivg**= -C_2H_5 **ivh**= C_3H_7 **ivi**=Ar-NH_2**ivj**=Phenyl

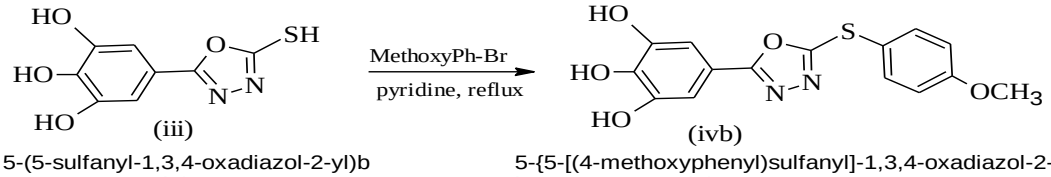
Step: 4.2 Synthesis of 5-{5-[(4-methylphenyl)sulfanyl]-1,3,4-oxadiazol-2-yl} benzene-1,2,3-triol **(iva)** for procedure refer step 3, aryl halide (4-methylbromo-benzene) was used.



(iii) 5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

(iva) 5-{5-[(4-methylphenyl)sulfanyl]-1,3,4-oxadiazol-2-yl} benzene-1,2,3-triol

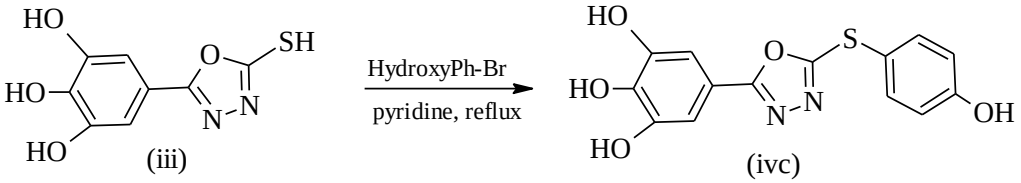
Step: 4.3 Synthesis of 5-{5-[(4-methoxyphenyl)sulfanyl]-1,3,4-oxadiazol-2-yl}benzene-1,2,3-triol**(ivb)** for procedure refer step 3, aryl halide (4-methoxylbromo benzene) was used.



(iii) 5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

(ivb) 5-{5-[(4-methoxyphenyl)sulfanyl]-1,3,4-oxadiazol-2-yl} benzene-1,2,3-triol

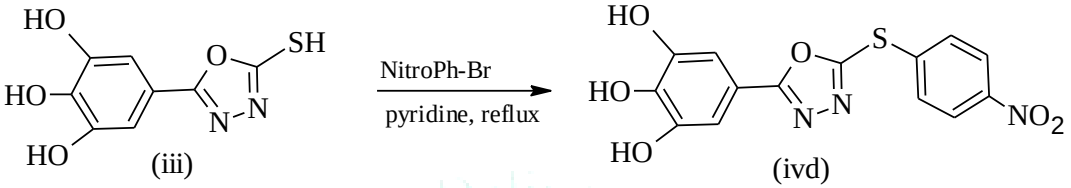
Step: 4.4 Synthesis of 5-{5-[(4-hydroxyphenyl)sulfanyl]-1,3,4-oxadiazol-2-yl}benzene -1,2,3-triol**(ivc)** for procedure refer step 3, aryl halide (4-hydroxy bromo benzene) was used.



5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

5-{5-[(4-hydroxyphenyl)sulfanyl]-1,3,4-oxadiazol-2-yl}benzene-1,2,3-triol

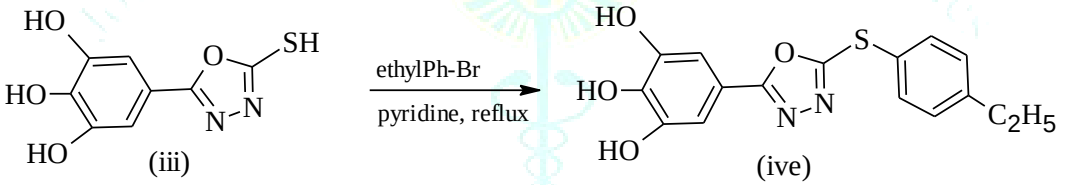
Step: 4.5 Synthesis of 5-{5-[(4-nitrophenyl)sulfanyl]-1,3,4-oxadiazol-2-yl}benzene-1,2,3-triol **(ivd)** for procedure refer step 3, aryl halide (4-nitro-bromobenzene) was used



5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

5-{5-[(4-nitrophenyl)sulfanyl]-1,3,4-oxadiazol-2-yl}benzene-1,2,3-triol

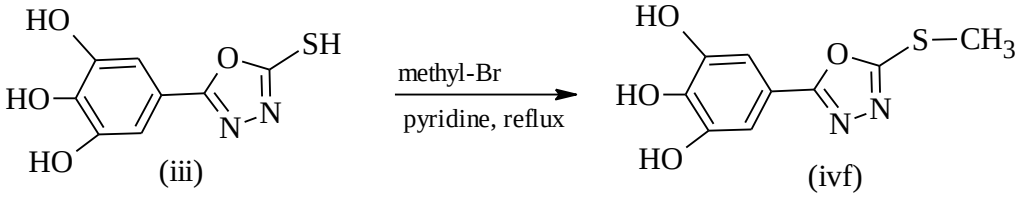
Step: 4.6 Synthesis of 5-{5-[(4-ethylphenyl)sulfanyl]-1,3,4-oxadiazol-2-yl}benzene-1,2,3-triol **(ive)** for procedure refer step 3, aryl halide (4-ethyl-bromo benzene) was used.



5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

5-{5-[(4-ethylphenyl)sulfanyl]-1,3,4-oxadiazol-2-yl}benzene-1,2,3-triol

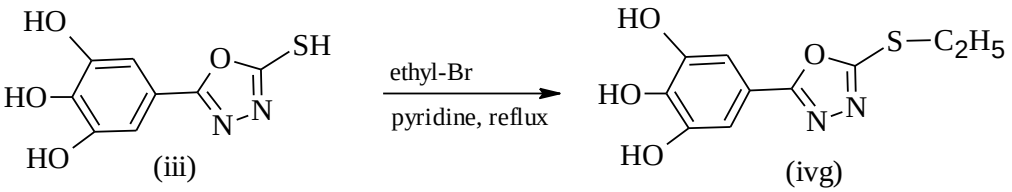
Step: 4.7 Synthesis of 5-[5-(methylsulfanyl)-1,3,4-oxadiazol-2-yl]benzene-1,2,3-triol **(ivf)** for procedure refer step 3 alkyl halide (methyl-bromo) was used.



5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

5-[5-(methylsulfanyl)-1,3,4-oxadiazol-2-yl]benzene-1,2,3-triol

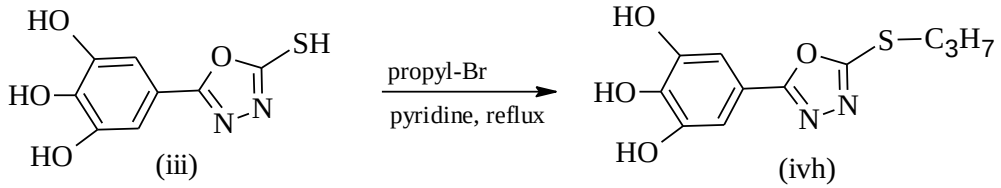
Step: 4.8 Synthesis of 5-[5-(ethylsulfanyl)-1,3,4-oxadiazol-2-yl]benzene-1,2,3-triol (ivg) for procedure refer step 3 alkyl halide (ethyl-bromo) was used.



5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

5-[5-(ethylsulfanyl)-1,3,4-oxadiazol-2-yl]benzene-1,2,3-triol

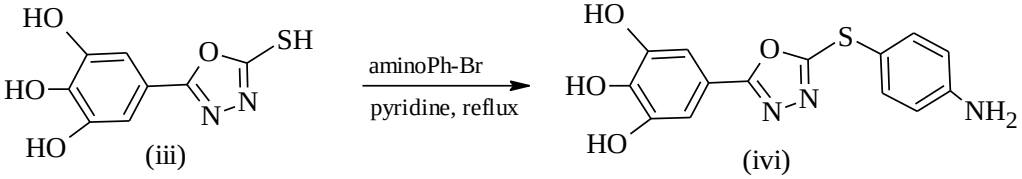
Step: 4.9 Synthesis of 5-[5-(propylsulfanyl)-1,3,4-oxadiazol-2-yl]benzene-1,2,3-triol (ivh) for procedure refer step 3 alkyl halide (propyl-bromo) was used



(iii) 5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

(ivh) 5-[5-(propylsulfanyl)-1,3,4-oxadiazol-2-yl]benzene-1,2,3-triol

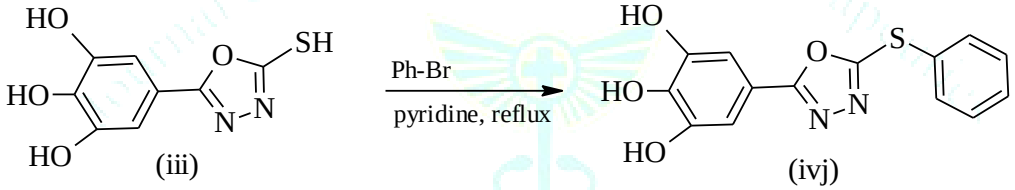
Step: 4.10 Synthesis of 5-{5-[(4-aminophenyl)sulfanyl]-1,3,4-oxadiazol-2-yl}benzene-1,2,3-triol **(ivi)** for procedure refer step 3, aryl halide (4-amino-bromo benzene) was used



(iii) 5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

(ivi) 5-{5-[(4-aminophenyl)sulfanyl]-1,3,4-oxadiazol-2-yl}benzene-1,2,3-triol

Step: 4.11 Synthesis of 5-[5-(phenylsulfanyl)-1,3,4-oxadiazol-2-yl]benzene-1,2,3-triol **(ivj)** for procedure refer step 3, aryl halide (bromo benzene) was used.



(iii) 5-(5-sulfanyl-1,3,4-oxadiazol-2-yl)benzene-1,2,3-triol

(ivj) 5-[5-(phenylsulfanyl)-1,3,4-oxadiazol-2-yl]benzene-1,2,3-triol

Table 1 physiochemical data of synthesized compound (iva-j)

Compound	% yield	Rf value	Mol. formula	Mol. weight
iva	81.64	0.63	$C_{15}H_{12}N_2O_4S$	316.33
ivb	73.27	0.82	$C_{15}H_{12}N_2O_5S$	332.33
ivc	77.33	0.74	$C_{14}H_{10}N_2O_5S$	318.30
ivd	61.01	0.79	$C_{14}H_{19}N_3O_6S$	347.30
ive	69.82	0.81	$C_{16}H_{14}N_2O_4S$	330.35
ivf	78.62	0.58	$C_9H_8N_2O_4S$	240.23
ivg	76.23	0.68	$C_{10}H_{10}N_2O_4S$	254.26
ivh	65.73	0.66	$C_{11}H_{12}N_2O_4S$	268.28
ivi	71.98	0.85	$C_{14}H_{11}N_3O_4S$	317.31
ivj	91.82	0.71	$C_{14}H_{10}N_2O_4S$	302.30

Solvent system for TLC- ethyl acetate: n-hexane (65:35)

Screening of Antibacterial Activity:

All the compounds synthesized in the present investigation were screened for their anti-bacterial activity by Cup plate Method. Antibacterial activities were tested on nutrient medium against, Staphylococcus aureus, and Escherchia coli which are representative types of gram positive and gram negative organisms respectively. The antibacterial activity of the compounds was assessed by disc-diffusion method.

Preparation of Nutrient Agar Media:

Media Composition and Procedure:

The nutrient agar media was prepared by using the following ingredients.

1) Peptone (Bacteriological) 20 gm
2) Beef extract (Bacteriological) 5 gm
3) Sodium chloride 5 gm
4) Agar Agar 20 gm
5) Distilled water up to 1000 ml.

Weighed quantities of peptone and beef extract were dissolved in distilled water by gentle warming and then

specified amount of agar was dissolved by heating on water bath. Then the pH of the solution was adjusted to7.2 to7.4 by adding the sodium chloride and the volume of the final solution was made up to 1000 ml with distilled water. Then it was transferred in to a suitable container, plugged with non-adsorbent cotton and the media was sterilized by in autoclave at 121^{0}C for 20 minutes at 15 lbs pressure.

Preparation of Test Solutions:

10 mg of the compound was dissolved in 10 ml of DMF. From this 1 ml of solution was taken and diluted up to 10 ml with DMF. Now the concentration of the test solution was 100 µg/ml. From the stock solution 1ml of solution was taken and diluted with 1ml of DMF now the concentration is 50µg/ml.

Preparation of standard antibiotic solution:

Amoxicillin was used as standard antibiotics for comparison and solutions were prepared by using sterile water, as they were water-soluble. The solutions are diluted by using sterile water so that the concentrations of the solutions were 100 µg/ml and 50 µg/ml.

Preparation of Discs:

Discs of 6-7 mm in diameter were punched from NO: 1 Whattmann filter paper with sterile cork borer of same size. These discs were sterilized by keeping in oven at 140^{0}C for 60 minutes. Then standard and test solutions were added to each disc and discs were air-dried.

Method of Testing:

The sterilized media was cooled to 45^{0}C with gentle shaking to bring about uniform cooling and then inoculated with 18-24 hrs old culture under aseptic conditions, mixed well by gentle shaking. This was poured in to sterile Petri dishes (properly labeled) and allowed the medium to set. After solidification all the Petri dishes were transferred to laminar flow unit. Then the discs which were previously prepared were carefully kept on

the solidified media by using sterilized forceps. These Petri dishes were kept as it is for one-hour diffusion at room temperature and then for incubation at 37^{0}C for 24 hours in an incubator.

The extent diameter of inhibition after 24 hours was measured as the zone of inhibition in millimeters.

RESULT AND DISCUSSION:

Table 1: anti-bacterial activity data of synthesized compounds

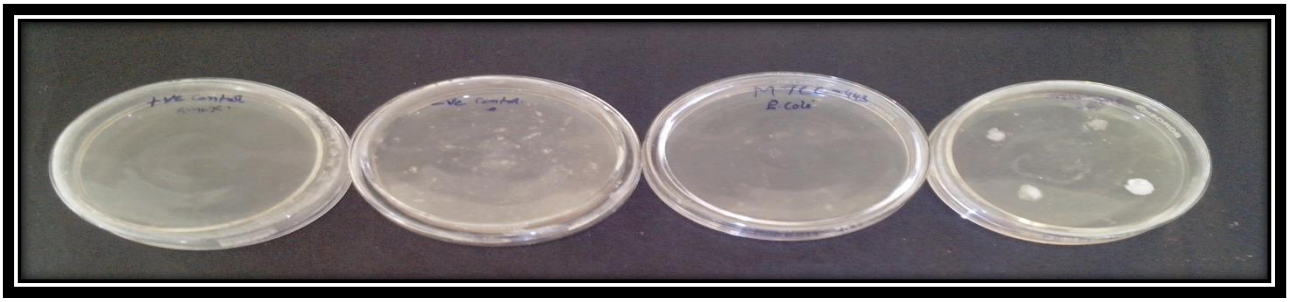
Sr.No	compound	Concentration µg/ml	*E.coli*	*S.Aureus*
1	iva	50	9	10
		100	11	10
2	ivb	50	9	11
		100	12	11
3	ivc	50	9	10
		100	13	14
4	ivd	50	10	12
		100	13	14
5	ive	50	10	11
		100	12	12
6	ivf	50	9	8
		100	10	9
7	ivg	50	11	11
		100	13	12
8	ivh	50	10	9
		100	11	10
9	ivi	50	20	19
		100	22	22
10	ivj	50	10	11
		100	11	12
11	Amoxicillin	50	24	25
		100	25	25

Zone of inhibition of synthesized compounds:

Note: 6-8 mm poor activity, 9-11 mm moderate activity, 12-15 above good.

Strain of *E.Coli* **strain of *S.Aureus*** **strain of *E.Coli*** **strain of *S.Aureus***

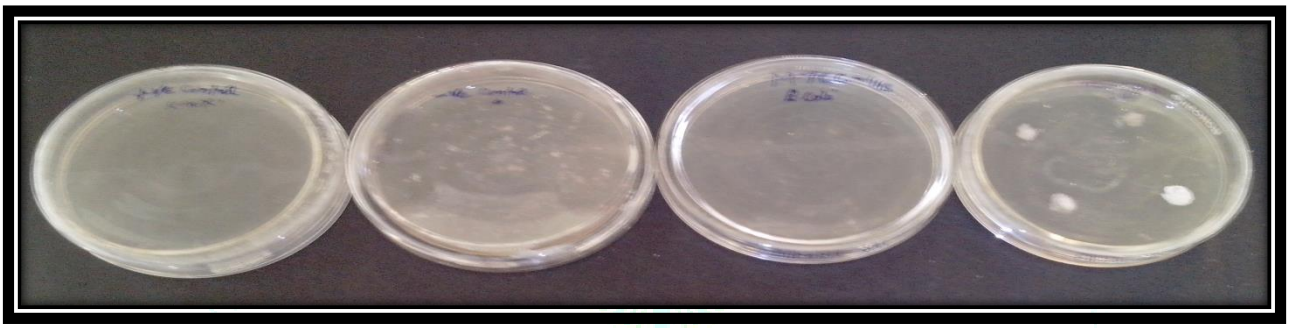
Conc. 50µg/ml **Conc.** 100µg/ml



(Zone of inhibition of comp iva)

Strain of *E.Coli* **strain of *S.Aureus*** **strain of *E.Coli*** **strain of *S.Aureus***

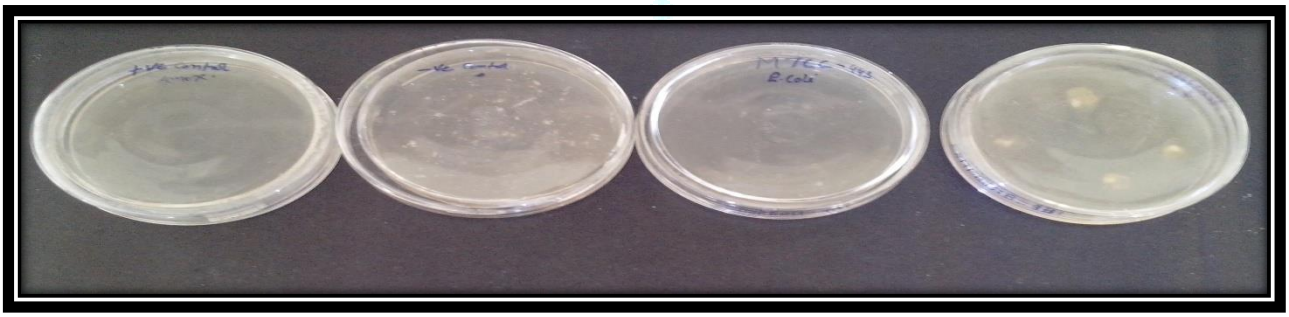
Conc. 50µg/ml **Conc.** 100µg/ml



(Zone of inhibition of comp ivb)

Strain of *E.Coli* **strain of *S.Aureus*** **strain of *E.Coli*** **strain of *S.Aureus***

Conc. 50µg/ml **Conc.** 100µg/ml



(Zone of inhibition of comp ivc)

Fig: 5.18 -Petri dish of compound iva to ivc

Strain of *E.Coli* **strain of *S.Aureus*** **strain of *E.Coli*** **strain of *S.Aureus***

Conc. 50µg/ml **Conc.** 100µg/ml

(Zone of inhibition of comp ivd)

Strain of *E.Coli* **strain of *S.Aureus*** **strain of *E.Coli*** **strain of *S.Aureus***

Conc. 50µg/ml **Conc.** 100µg/ml

(fig:5.16 Zone of inhibition of comp ive)

Strain of *E.Coli* **strain of *S.Aureus*** **strain of *E.Coli*** **strain of *S.Aureus***

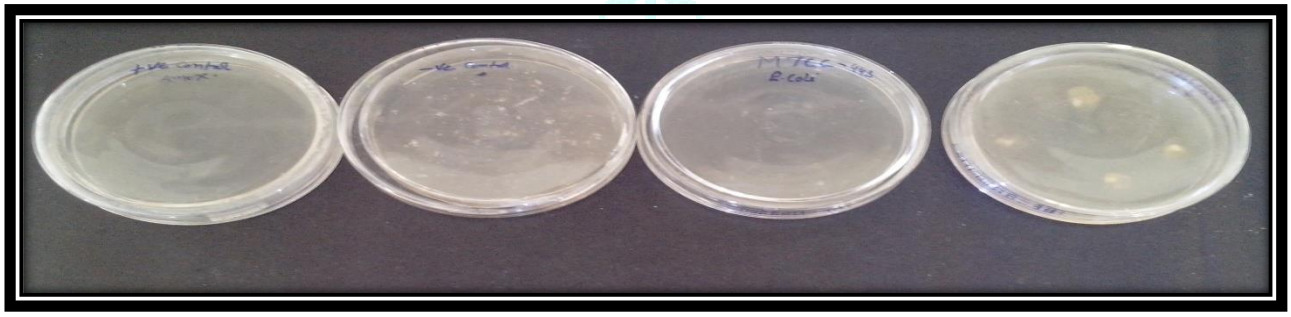
Conc. 50µg/ml **Conc.** 100µg/ml

(Zone of inhibition of comp ivf)

Fig: 5.19 -Petri dish of compound ivd to ivf

Strain of *E.Coli* **strain of *S.Aureus*** **strain of *E.Coli*** **strain of *S.Aureus***

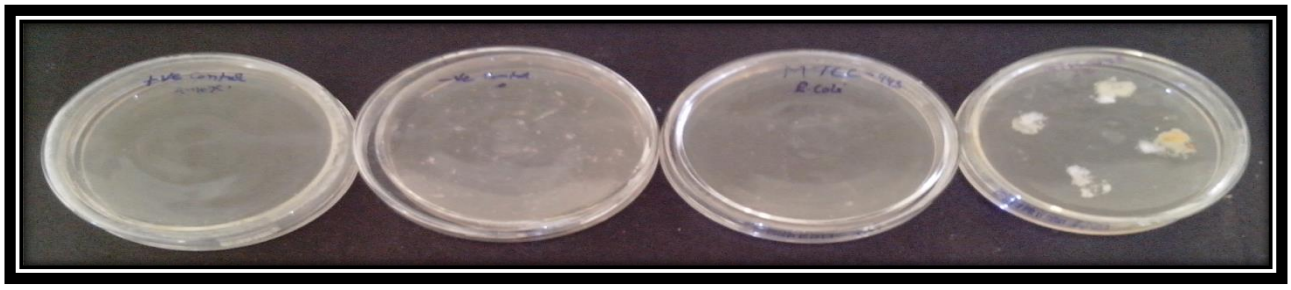
Conc. 50µg/ml **Conc.** 100µg/ml



(Zone of inhibition of comp ivg)

Strain of *E.Coli* **strain of *S.Aureus*** **strain of *E.Coli*** **strain of *S.Aureus***

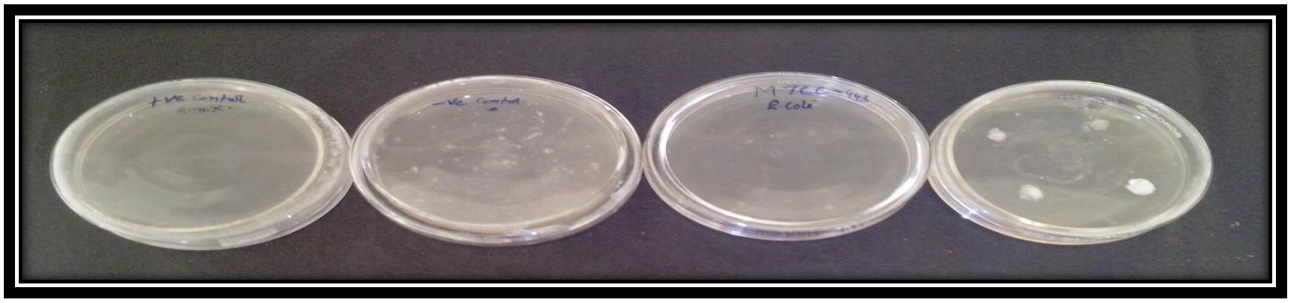
Conc. 50µg/ml **Conc.** 100µg/ml



(Zone of inhibition of comp ivh)

Strain of *E.Coli* **strain of *S.Aureus*** **strain of *E.Coli*** **strain of *S.Aureus***

Conc. 50µg/ml **Conc.** 100µg/ml

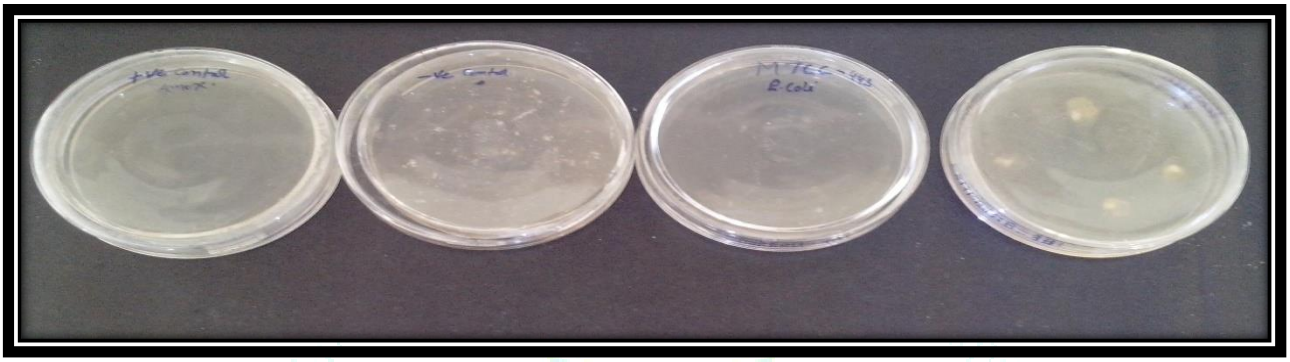


(Zone of inhibition of comp ivi)

Fig: 5.20 -Petri dish of compound ivg to ivi

Strain of *E.Coli* **strain of *S.Aureus*** **strain of *E.Coli*** **strain of *S.Aureus***

Conc. 50µg/ml **Conc.** 100µg/ml



(Zone of inhibition of comp ivb)

Strain of *E.Coli* **strain of *S.Aureus*** **strain of *E.Coli*** **strain of *S.Aureus***

Conc. 50µg/ml **Conc.** 100µg/ml

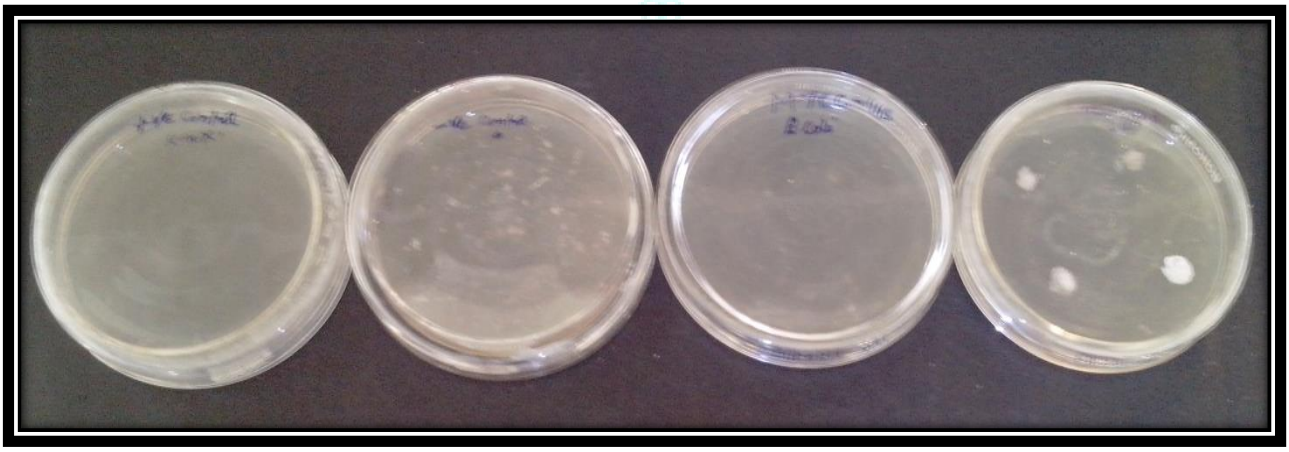


Fig: 5.21 -Petri dish of compound ivj & Amoxicillin(Standard)

CONCLUSION:

All the synthesized compounds were light creamish to brown coloured crystalline solids. Most of the compounds are freely soluble in chloroform and other solvents like methanol, ethanol. The melting point of the compounds was in the range of 152ºC to 251ºC. All synthesize compounds were tested for the preliminary tests, physical constants and TLC. All structures of final compound were confirmed by IR and ^{1}HNMR spectra as well as Mass spectra. Determination of Zone of inhibition of synthesized compounds against amoxicilline as standard compound were used compound **ivi** was near to significant with standard compound.

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