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Novel Synthesis and Characterization of Some Chlorosubstituted Aryl Substituted 1,3-Thiazole as Antibacterial Agents

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Abstract:
The synthesis, spectral analysis and biological activities of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-heptan-1-one- 2-[4-(2-hydroxy-3,5-dichlorophenyl)-2-mercapto-imidazolo]-1,3-thiazole ($8d_2$) (J") have been carried out. In this case 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(heptan-1-one)-2- amino-1,3-thiazole (8d) (J), 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-heptan-1-one-2-[(2-hydroxy-3,5-dichlorophenyl) ethanonylamino]-1,3-thiazole ($8d_1$) (J') & 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-heptan-1-one- 2-[4-(2-hydroxy-3,5-dichlorophenyl)-2-mercapto-imidazolo]-1,3-thiazole ($8d_2$) (J") have been screened. The compound (J) was synthesized from 1-(2'-Hydroxy-3',5'-dichlorophenyl)-2-bromo-1,3-nonanedione (a_4) by the action of thiourea, while (J") was synthesized from (J) by reaction with α-bromo, 2-hydroxy-3,5 dichloroacetophenone to get 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-heptan-1-one-2-[(2-hydroxy-3,5-dichlorophenyl)ethanonylamino]-1,3-thiazole ($8d_1$) (J'). Further (J') on treatment with KSCN was dissolved in acetic acid gave (J''). The nanoparticles of the compounds J, J'and J'' have been prepared by using ultrasonic technique. The newly synthesized titled compound and it's nanoparticles were screened for their antibacterial activity against some pathogens ; Gram+ve bacteria viz. Staphylococcus pneumoniae, Staphylococcus aureus and Gram-ve bacteria viz. Escherichia coli and Pseudomonas fluorescens by using agar disc diffusion method.All the newly synthesized compounds were found to be active against test pathogens.

Keywords: Chalcone, thiazine, thiourea, α-bromo,2-hydroxy-3,5 dichloroacetophenone, KSCN was dissolved in acetic acid, antibacterial assay.

INTRODUCTION:

Heterocyclic nucleus plays an important role in medicinal chemistry and it is a key template for the growth of various therapeutic agents. Thiazole is a heterocyclic compound featuring both a nitrogen atom and sulfur atom as part of the aromatic five-membered ring. Thiazoles and related compounds are called1,3-azoles (nitrogen and one other hetero atom in a five-membered ring). They are isomeric with the 1,2-azoles, the nitrogen and sulphur containing compound being called isothiazoles. Thiazoles are found naturally in the essential vitamins. Molecules that possess sulfur atoms are important in living organisms. Chalcones and their analogues having α, β-unsaturated carbonyl system are very versatile substrates for the evolution of various reactions and physiologically active compounds. Plant Pathology

or Phytopathology deals with the cause, etiology, resulting losses and control or management of the plant diseases.

. It is the scientific study of diseases in plants caused by pathogens (infectious organisms) and environmental conditions (physiological factors). Organisms that cause infectious disease include *fungi*, *oomycetes*, *bacteria*, *viruses*,*phytoplasmas*, *protozoa*, *nematod-es* and *parasitic plants.*
The researchers[1-6] have reported the synthesis of several thiazoles and also their potent biological activities such as antimicrobial[7], antibacterial[8], antifungal[9], fungicidal[10] and insecticidal agent[11].

Now a days nanotechnology is a promising field of interdisciplinary research. It opens up a wide array of opportunities in various fields like medicine, pharmaceuticals, electronics and agriculture.

Since the physiochemical properties of nanoforms vary greatly, it becomes important to examine the effect of nanoparticles on microorganisms to harness the benefit of this technology in the plant protection especially against phytopathogens. Previous studies confirmed that metal nanoparticles are effective against pathogens, insects and pests. Hence nanoparticles can be used in the preparation of new formulations like nanomedicines for the diseases like diagnosing & treating cancer[12], enhancing outer membrane of living cells[13], inhibiting tumour growth in human being[14], brain cancer [15]. Nanotechnology has the potential to revolutionize the different sectors of agriculture and food industry with modern tools for the treatment of diseases by providing the medicines for rapid diseases like malaria[16], cancer & HIV[17], breast cancer[18], localized diseases[19].

In the present study, the chlorosubstituted 1,3-thiazole & their imidazole derivatives (J") have been prepared along with their nanoparticles and screened them for their antibacterial activities against some Gram+ve bacteria viz. Staphylococcus pneumoniae, Staphylococcus aureus and Gram-ve bacteria viz. Escherichia coli and Pseudomonas. All the newly synthesized compounds were found to be active against test pathogens.

EXPERIMENTAL:-

All the glasswares used in the present work were of pyrex quality. Melting points were determined in hot paraffin bath and are uncorrected. The purity of compounds was monitored on silica gel coated TLC plate. IR spectra were recorded on Perkin-Elmer spectrophotometer in KBr pelletes, H^1 NMR spectra on spectrophotometer in $CDCl_3$ with TMS as internal standard. UV spectra were recorded in nujol medium. The analytical data of the titled compounds was highly satisfactory. All the chemicals used were of analytical grade. All the solvents used were purified by standard methods. Physical characterisation data of all the compounds is given in Table 1.

2'-Hydroxy 3,5'-Dichloroacetophenone:

2-Hydroxy-5-chloroacetophenone was dissolved in acetic acid (5 ml), Sodium acetate (3g) was added to the reaction mixture and then chlorine in acetic acid reagent (40 ml; 7.5 w/v) was added dropwise with stirring. The temperature of the reaction mixture was maintained below 20^0C. The mixture was allowed to stand for 30 minutes. It was poured into cold water with stirring. A pale yellow solid then obtained was filtered, dried and crystallized from ethanol to get the compound 2'-hydroxy 3',5'-dichloroacetophenone.

Preparation of 2'-hydroxy-3',5'-dichloro-4-hexylchalcone :

2-Hydroxy-3,5-dichloroacetophenone (0.01 mol) dissolved in ethanol (50 ml) treated with heptanaldehyde (0.1 M) at its boiling temperature. Aqueous sodium hydroxide solution [40%, 40 ml] was added dropwise and the the mixture was stirred mechanically at room temperature for about 1 hour. It is then kept for 6 to 8 hours followed by decomposition with ice cold HCl [1:1]. The yellow granules thus obtained were filtered, washed with 10% $NaHCO_3$ solution and finally crystallized from ethanol-acetic acid solvent mixture to get the compound .

Preparation of 1-(2'-hydroxy-3'-5'-dichlorophenyl)-2,3-dibromononan-1-one (a_1) :

2'-Hydroxy-3',5'-dichloro-4-hexylchalcone (0.01 M) was suspended in bromine–glacial acid reagent [25% w/v] [6.4 ml]. The reagent was added dropwise with constant stirring. After complete addition of reagent the reaction mixture was kept at room temperature for about 30 minutes. The solid product, thus separated, was filtered and washed with a little petroleum ether to get the compound (a_1).

Preparation of 2-(4"-hexyl)- 6,8-dichloroflavone (a_2):

1-(2'-Hydroxy-3',5'-dichlorophenyl)-2,3-dibromo-nonan-1-one (0.01 mol) was dissolved in ethanol (25 ml). To this, aqueous solution of KOH (25 ml) was added. The reaction mixture was refluxed for 1 hour, cooled and diluted with water. The product, thus separated, was filtered and crystallized from ethanol to get the compound (a_2).

Preparation of 1-(2'-hydroxy-3',5'-dichlorophenyl)-1,3-nonanedione (a_3) :

2-(4"-Hexyl)-6,8-dichloroflavone (0.01 mol) was dissolved in ethanol (25 ml). To this, aqueous solution of HCl (25 ml) was added. The reaction mixture was then refluxed for one hour, cooled and diluted with water. The solid product, thus obtained, filtered and crystallized from ethanol to get the compound (a_3).

Preparation of 1-(2'-hydroxy-3',5'-dichlorophenyl)-2-bromo-1,3-nonanedione (a_4) :

1-(2'-Hydroxy-3',5'-dichlorophenyl)-1,3-nonanedione (0.01 mol) was dissolved in a mixture of ethanol (10 ml) and dioxane (10 ml). To this, calculated amount of liquid bromine (0.5 ml) was added. The product was not separated even after standing for one hour. It was then diluted with water and washed with water several times and extracted with ether. The solvent was removed under reduced pressure to get the white solid of the compound (a_4).

Preparation of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(heptan-1-one)-2- amino-1,3-thiazole (J) :

1-(2'-Hydroxy-3',5'-dichlorophenyl)-2-bromo-1,3-nonanedione (a_4) (0.01 mol) and thiourea (0.01 mol) were dissolved in ethanol (25 ml). To this, aqueous KOH solution (0.01 mol) was added. The reaction mixture was then refluxed for three hours, cooled, diluted with water and acidified with conc HCl. The product, thus separated, was filtered and crystallized from ethanol to get the compound (J).

Preparation of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-heptan-1-one-2-[(2-hydroxy-3,5-dichlorophenyl)ethanonylamino]-1,3-thiazole (J'):

A stoichiometeric mixture of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(heptan-1-one)-2- amino-1,3-thiazole (J) and α-bromo-2-hydroxy-3,5-dichloro acetophenone was dissolved in ethanol and

refluxed for one hour. It was then cooled, diluted with water and crystallized from ethanol to get the compound (J').

Preparation of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-heptan-1-one- 2-[4-(2-hydroxy-3,5-dichlorophenyl)-2-mercapto-imidazolo]-1,3-thiazole (J"):

A stoichiometeric mixture of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-heptan-1-one-2-[(2-hydroxy-3,5-dichlorophenyl)ethanonylamino]-1,3-thiazole(J') and KSCN was dissolved in acetic acid, refluxed for 4.5 hours, cooled ,diluted with water,and solid product, thus obtained crystallized from ethanol to get the compound (J")**.**

The UV, IR, and NMR spectral data :-

Compound (J) :

UV : Spectrum No. 1

The UV-Vis spectrum of the compound (J) reported in dioxane showed λ_{max} value 410 nm corresponding to $n \rightarrow \pi^*$ transition.

IR (KBr) :- Spectrum No. 2

3036.60 cm^{-1} (-OH phenolic), 2955.55cm^{-1} (aliphatic -C-H stretching), 3036.60cm^{-1} (aromatic -C-H stretching), 3797.72 cm^{-1} (-NH_2 stretching), 1538.48 cm^{-1} (-C=N stretching), 1228.56 cm^{-1} [(C-N=) stretching], 756.57 cm^{-1} (C-Cl stretching in aliphatic), 1073.66 cm^{-1} (C-Cl) stretching in aromatic).

PMR :- Spectrum No. 3

∂ 5.2 (hump, 2H, -N-**H**$_2$) ; ∂ 6.7 (d, 1H, -CH=C-**H**) ; ∂ 6.8 (d, 1H, -C**H**=C-H) ; ∂ 7 to 7.8 (m, 6H, Ar-**H**) ; offset (region not observed, observed, O-**H**)

Compound (J'') :

UV : Spectrum No. 4

The UV-Vis spectrum of the compound J" reported in dioxane showed λ_{max} value 399 nm corresponding to $n \rightarrow \pi^*$ transition.

IR (KBr) :- Spectrum No. 5

1649 cm^{-1} (=C=O stretching), 3391 cm^{-1} (-OH phenolic), 2925 cm^{-1} (aliphatic -C-H stretching), 3068 cm^{-1} (aromatic -C-H stretching), 1435.8 cm^{-1} (-C=N stretching), 1305 cm^{-1} [(C-N) (C-NO_2) stretching], 738 cm^{-1} (C-Cl stretching in aliphatic), 2547 cm^{-1} (-S-H stretching).

1.02

PMR :- Spectrum No. 6

∂ 7.4 to 8.25 (m, 4H, Ar-**H**) ; ∂ 0.80 (t, 3H, -CH2-C**H**3**,** ∂ 1.064 (envelope of CH2, **10H,** -(CH2)-C**H3).**

Preparation of Nanoparticles of the Titled Compound:

Ultrasonic Processor Sonapros PR-250MP was used to produce nanoparticles of the test compound. The test compound was dissolved in dioxane to prepare 0.1 M solutions. This solution was taken in a beaker and the probe of the sonapras 250 MP was dipped in solution. These solution was exposed to sonopros MP 250 for 10 minutes separately. The test compound was converted to nanoparticles. The solvent

dioxane was evaporated by conventional heating method. The size of nanoparticles of the test compound was confirmed by X-ray diffraction studies using Benchtop x-ray diffraction (XRD) instrument **(**Miniflex).

The thin film of the nanoparticles of the test compound was prepared on glass slide. This slide was intr oduced to the X-ray diffraction instrument to get graphical information which was used for the calculation of the crystal size of test compounds.

Characterisation of Size of Nanoparticles of the Test Compound:

The crystal size of nanoparticles of the test compound is calculated by using Debye -Scherrer equation.

$$D = \frac{0.94\,\lambda}{\beta \cdot \cos\theta}$$

Where,

D = The average crystalline size.

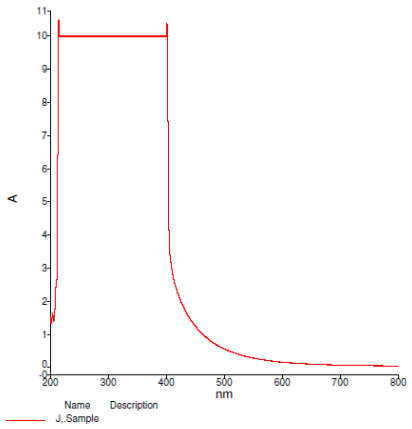
0.94 = The particle shape factor which depends on the shape and size of the particle.

λ = is the wavelength.

□ = is the full width at half maximum [FWHM] of the selected diffraction peaks (β = 0.545)

□ = is the Bragg's angle obta ined from 2θ va lues which was corresponding to the maximum intensity peak

in XRD pattern (□ = 0.7501 rad).



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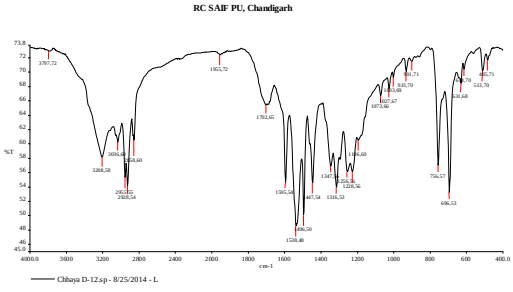

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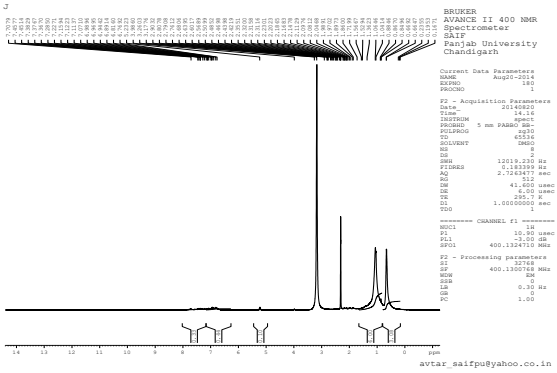

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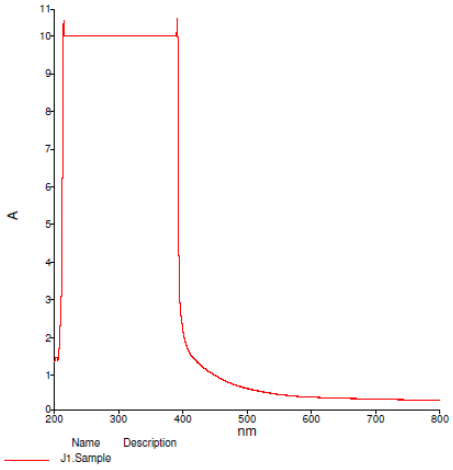

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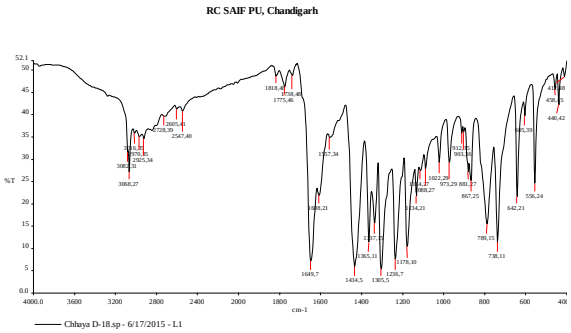

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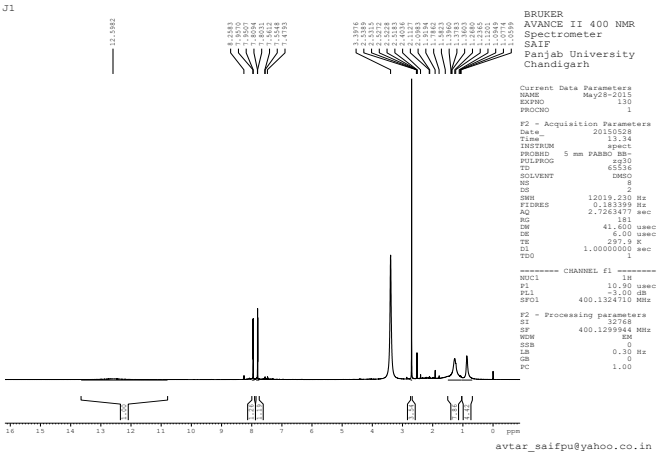
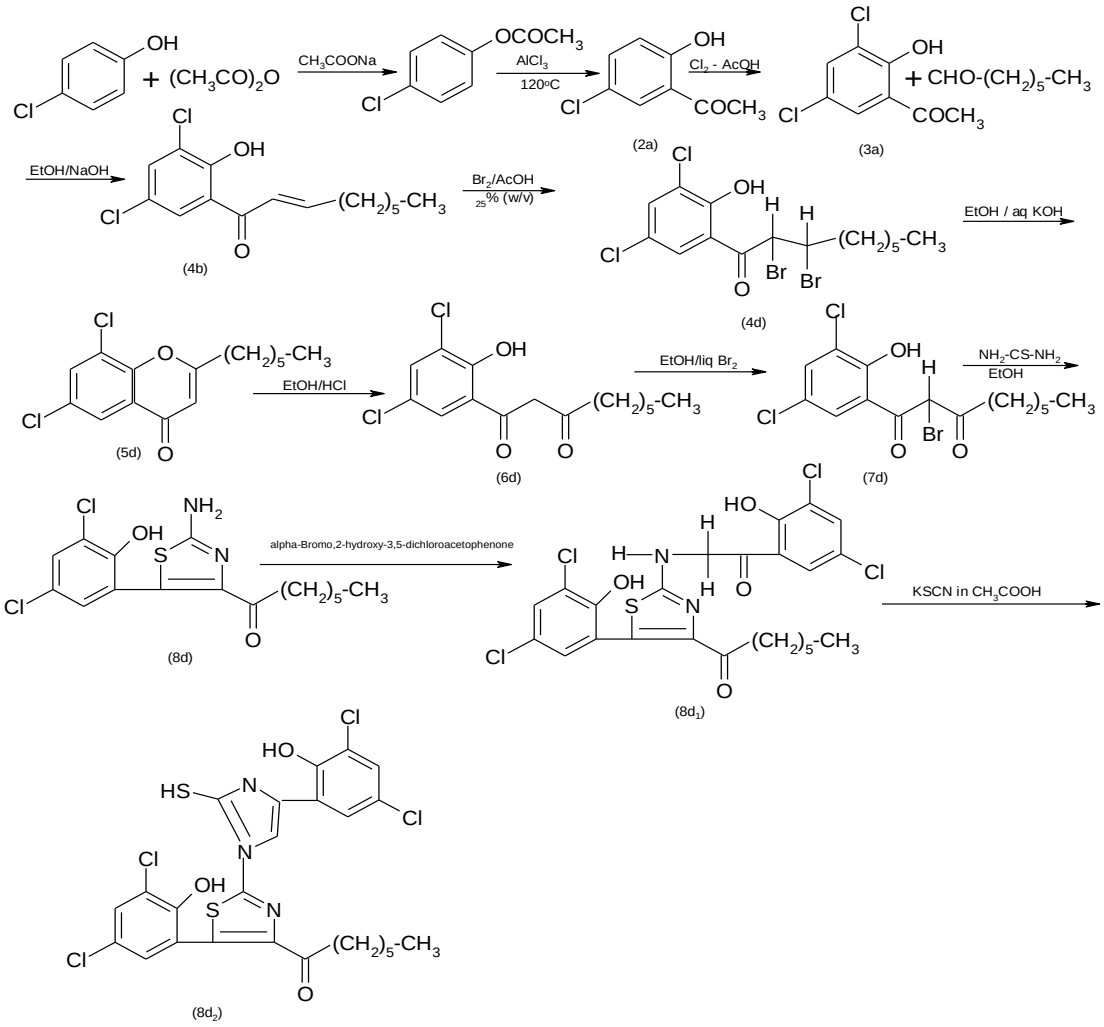


Spectrum No. 06

Table 1 : Characterisation data of newly synthesized compounds :

Compounds	Molecular formula	M.P. in ^0C	% of yield	% of element					
				C	H	N	S	Cl	Br
	$C_8H_6O_2Cl_2$	54	80	47.90/48	2.95/3			34.15/34.58	
a	$C_{15}H_9O_4NCl_2$	250	70	53.10/53.25	2.40/2.66	3.98/4.18		21/21.77	
a_1	$C_{15}H_9O_4NCl_2Br_2$	72	70	36.01/36.14	1.78/1.80	2.78/2.81		14.20/14.25	32.08/32.12
a_2	$C_{15}H_7O_4NCl_2$	132	60	53.14/53.57	2.07/2.08	4.13/4.16		21.03/21.13	
a_3	$C_{15}H_9O_5NCl_2$	117	50	50.74/50.84	2.45/2.54	3.90/3.95		20.03/20.05	
a_4	$C_{15}H_8O_5NCl_2Br$	78	60	41.12/41.57	1.78/1.84	3.20/3.23		16.08/16.39	18.34/18.47
J	$C_{16}H_{20}O_2N_2Cl_2S$	96	60	51.10/51.20	5.30/5.33	7.40/7.46	7.67/7.76	17.20/17.23	
J’	$C_{24}H_{22}O_4N_2Cl_4S$	94	70	49.85/50.00	3.78/3.81	4.78/4.86	5.50/5.55	24.50/24.65	
J”	$C_{25}H_{21}O_3N_3Cl_4S_2$	108	70	48.60/48.62	3.38/3.40	6.75/6.80	10.35/10.37	23.00/23.01	

Scheme :



Where :

1) R_1 = -H, -C_6H_5
2) R_2 = -H, -C_6H_5

EXPERIMENTAL DETAILS AND DISCUSSION OF RESULTS :

Antibacterial Assay :

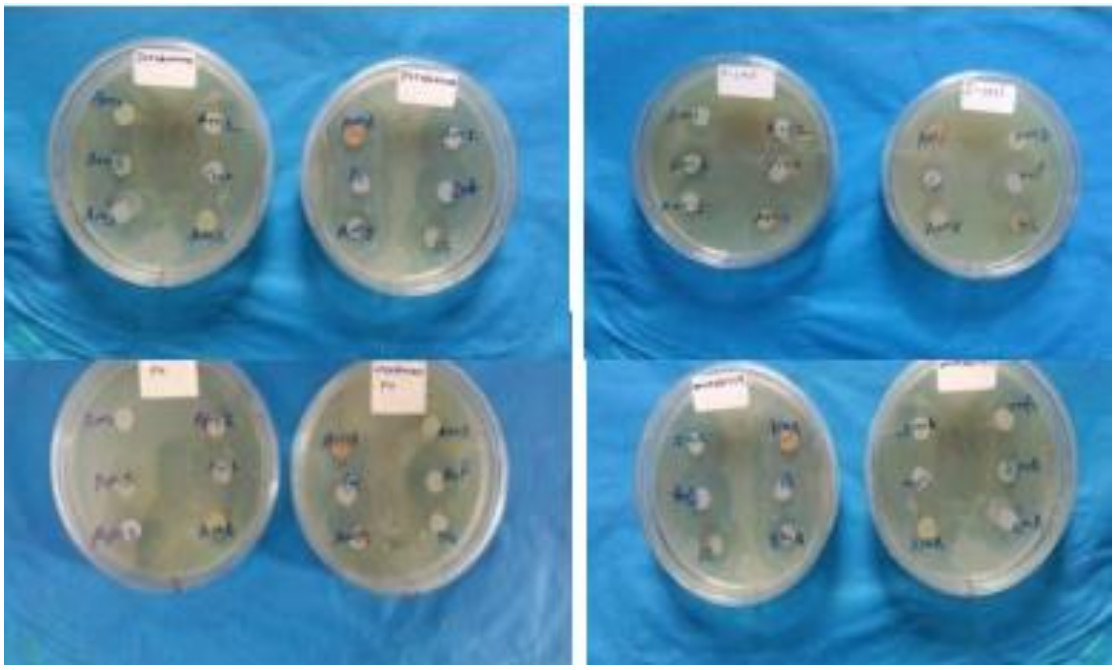
The compounds (a – J") were screened for their antibacterial activity against Gram +ve bacteria viz. Staphylococcus pneumoniae, Staphylococcus aureus and Gram -ve bacteria viz. Escherichia coli and Pseudomonas fluorescens at conc. of 1000 ppm by using Agar disc diffusion method. Ofloxacin used as a standard and chloroform as solvent control. The zones of inhibition formed were measured in mm and are shown in Table No.2.

Table No.2- Impact of test compounds against plant pathogens :

Sample Code	(Gram positive)		(Gram Negative)	
	Staphylococcus pneumoniae	Staphylococcus aureus	Escherichia coli	Pseudomonas fluorescens
a	**-**	**15**	**12**	**12**

a_1	**-**	**13**	**-**	**12**
a_2	**17**	**14**	**12**	**15**
a_3	**15**	**-**	**12**	**25**
a_4	**14**	**12**	**15**	**12**
J	**14**	**15**	**15**	**-**
J'	**12**	**13**	**12**	**18**
J"	**12**	**-**	**14**	**25**
Reference Antibiotic	(Ofloxacin)	(Ofloxacin)	(Ofloxacin)	(Ofloxacin)

Diameter of inhibition zone (mm)



RESULT AND DISCUSSION :

Most of the test compounds have shown remarkable and very encouraging antibacterial activities. A further detailed study in the light of plant pathology is advised.

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