EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 6
Issue: 2
299-304
Year: 2019

SYNTHESIS OF IMIDAZOLE DERIVATIVES OF ARYL SUBSTITUTED 1,3-THIAZOLES AND THEIR NANOPARTICLES WITH SPECIAL REFERENCE TO PLANT PATHOGENS OF SOME VEGETABLE CROPS

Chhaya D. Badnakhe*[1] and P. R. Rajput[2]

[1]Department of Chemistry, Dr.Manorama and Prof.H.S.Pundkar, Arts, Commerce and Science College, Balapur, Dist. Akola.
[2]Department of Chemistry,Vidyabharti Mahavidyalaya, Amravati-444604. India.

***Corresponding Author: Dr. Chhaya D. Badnakhe**
Department of Chemistry, Dr.Manorama and Prof.H.S.Pundkar, Arts, Commerce and Science College, Balapur, Dist. Akola.

Article Received on 02/12/2018 **Article Revised on 23/12/2018** **Article Accepted on 15/01/2019**

ABSTRACT
The synthesis, spectral analysis and biological activities of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4"-nitrobenzoyl)-2-(3N-phenyl)-[4-(2-hydroxy-3,5-dichlorophenyl)-2-mercapto-imidazolo]-1,3-thiazole (F") have been carried out. In this case 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4"-nitrobenzoyl)-2-diphenyl-amino-1,3-thiazole (F), 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4"-nitrobenzoyl)-2-(N-phenyl)-[(2-hydroxy-3,5-dichlorophenyl)ethanonylamino]-1,3-thiazole (F') & 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4"-nitrobenzoyl)-2-(3N-phenyl)-[4-(2-hydroxy-3,5-dichlorophenyl)-2-mercapto-imidazolo]-1,3-thiazole (F'') have been screened. The compounds (F), and was synthesized from 1-(2'- hydroxy-3',5'-dichlorophenyl)-2-bromo-3-(4"-nitrophenyl)-1,3 propanedione (a_4) by the action of diphenyl thiourea, while (F'') was synthesized from (F) by reaction with α-bromo,2-hydroxy-3,5 dichloroacetophenone to get 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4"-nitrobenzoyl)-2(N-phenyl)-[(2-hydroxy-3,5-dichlorophenyl)ethanonylamino]-1,3-thiazole (F'). Further (F') on treatment with KSCN was dissolved in acetic acid gave (F''). The nanoparticles of the compounds F, F'and F'' have been prepared by using ultrasonic technique. The titled compounds and their nanoparticles were assayed for antipathogenic impact against some common crop pathogens viz - *Aspergillus niger, Pseudomonas lachrymans, Fusarium oxysporum* and *Fusarium solani.*

KEYWORDS: Chalcone, thiazine, diphenyl thiourea, α-bromo,2-hydroxy-3,5 dichloroacetophenone , KSCN was dissolved in acetic, antipathogenic activities.

INTRODUCTION
Heterocyclic nucleus plays an important role in medic inal chemistry and it is a key template for thegrowth of var ious therapeutic agents. Thiazole is a heterocyclic compound featuring both a nitrogen atom and sulfur atom as part of the aromatic f ive-membered ring. Thia zoles 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 be in g 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 var ious reactions and phys iologically 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, nematodes* 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], antidiabetic & fungicidal[10] and antioxidant agent.[11]

Nanotechnology is a joint interdisciplinary programme of the following departments-Biological sciences, chemistry, physics, chemical engineering, electrical and electronics engineering, metallurgical and material engineering and mechanical engineering. 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. By the technique of "Top Down" approach (used to synthesize nanoparticles) the nanoparticles synthesized show the important properties like anticancer activity[12], diuretics[13], antiallergic[14], antifilarial activity.[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 inhibition of tomour cells proliferation[16], breast cancer[17], liver cancer[18], cancer & HIV.[19]

In the present study, the chlorosubstituted 1,3-thiazoles & their imidazole derivatives (F,F',F") have been prepared along with their nanoparticles and were assayed for antipathogenic impact against some common crop pathogens viz - *Aspergillus niger*, *Pseudomonas lachrymans*, *Fusarium oxysporum* and *Fusarium solani.*

EXPERIMENTAL

All the glasswares used in the present work were of pyrex qua lity. Melting points were determined in hot paraffin bath and are uncorrected. The purity of compounds was monitored on s ilica 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 med ium. The analytical data of the titled compounds was highly satisfactory. A ll 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 stirr ing. 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 stirr ing. A pale yellow solid then obta ined was filtered, dr ied and crystallized from ethanol to get the compound 2-hydroxy 3,5 -dichloroacetophenone.

Preparation of 2'-hydroxy-3',5'-dichlorophenyl-4-(4''-nitrophenyl) chalcone (a)

To the boiling solution of the 2-hydroxy-3,5-dichloroacetophenone (0.01 mol) and p-nitr obenza ldehyde (0.01 mol) in ethanol (20 ml) a 40% solution of NaOH was added gradually. The reaction mixture was stirred mechanically at room temperature for 1 hour and kept steady for 6 to 8 hours, followed by decompos ition w ith ice cold HCl (1:1). The yellow granules thus obtained were filtered, washed with 10% $NaHCO_3$ solution and then crystallized from ethanol-acetic acid mixture to obtain the compound (a).

Preparation of 1-(2'-hydroxy-3',5'-dichlorophenyl)-2,3-dibromo-3-(4"-nitrophenyl)-propan-1-one (a_1)

2'-Hydroxy- 3',5'- dichlorophenyl-4-(4"-nitrophenyl) cha lcone (a) (0.001 M) was suspended in br omine –glacial acetic acid reagent (25% w/v) (6.4 ml).

The reagent was added dropwise with constant stirring and 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"-nitrophenyl)-6,8-dichloroflavone (a_2):

1-(2'-Hydroxy- 3',5'-dichlorophenyl)-2,3-dibromo-3-(4"-nitrophenyl)-pr opan-1-one (a_1) (0.01 mol) was dissolved in ethanol (25ml). To this, aqueous KOH solution (25 ml) was added. The reaction mixture was refluxed for 1 hour , cooled and diluted w ith 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)-3-(4"-nitrophenyl)-1,3-propandione (a_3)

2-(4"-Nitrophenyl)-6,8-dichlor of lavone (a_2) (0.01 mol) was dissolved in ethanol (25ml). To this, aqueous solution of HCl (25 ml) was added. The reaction mixture was then refluxed for 1 hour , cooled, and diluted with water. The product, thus separated, was filtered, and crystallized from ethanol to get the compound (a3).

Preparation of 1-(2'-hydroxy-3',5'-dichlorophenyl)-2-bromo-3-(4"-nitrophenyl)-1,3 propanedione (a_4)

1-(2'-Hydroxy- 3',5'-dichlorophenyl)-3-(4"-nitrophenyl)-1,3-propandione (a_3) (0.01 mol) was dissolved in a mixture of ethanol and dioxane. To this, calc ulated amount of liquid bromine was added. The product was not separated even after standing for one hour. It was then diluted with water, 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-(4"-nitrobenzoyl)-2-diphenyl-amino-1,3-thiazole (F)

1-(2'-Hydroxy-3',5'-dichlorophenyl)-2-bromo-3-(4"-nitrophenyl)-1,3-propandione (a_4) (0.01 mol) and diphenyl thiourea (0.01 mol) were dissolved in ethanol (25 ml). To this aqueous solution of KOH (0.02 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 (F).

Preparation of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4"-nitrobenzoyl)-2-(N-phenyl)-[(2-hydroxy-3,5-dichlorophenyl)ethanonylamino]-1,3-thiazole (F')

A stoichiometeric mixture of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4"-nitrobenzoyl)-2-diphenyl-amino-1,3-thiazole (F) and α-bromo,2-hydroxy-3,5 dichloroacetophenone was dissolved in ethanol and refluxed for one hour. It was then cooled, diluted with water and crystallized from ethanol to get the compound (F').

Preparation of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4"-nitrobenzoyl)-2-(3N-phenyl)-[4-(2-hydroxy-3,5-dichlorophenyl)-2-mercapto-imidazolo]-1,3-thiazole (F"):

A stoichiometeric mixture of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(4"-nitrobenzoyl)-2-N-phenyl-[(2-hydroxy-3,5-dichlorophenyl)ethanonylamino]-1,3-thiazole (F') and KSCN were dissolved in acetic acid and refluxed for 4.5 hours, cooled and diluted with water. The product, thus separated, was crystallized from ethanol to get the compound (F").

The UV, IR, and NMR spectral data

Compound (F)

UV: Spectrum No. 1

The UV-Vis spectrum of the compound F reported in dioxane showed λ_{max} value 405 nm corresponding to n→π* transition.

IR (KBr): Spectrum No. 2

3025.30 cm^{-1} (-OH phenolic), 1445.6 cm^{-1} (-C=C stretching), 3035.11cm^{-1} (aromatic -C-H stretching), 1621.8 cm^{-1} (=C=O stretching), 1548 cm^{-1} (-C=N stretching), 1344cm^{-1} [(C-N=) stretching], 755.8 cm^{-1} (C-Cl stretching in aliphatic), 1072.15 cm^{-1} (C-Cl) stretching in aromatic).

PMR: Spectrum No. 3

∂ 6.9 (d, 1H, -CH=C-**H**) ; ∂ 6.93 (d, 1H, -C**H**=C-H) ; ∂ 7.07 to 8.6 (m, 16H, Ar-**H**) ; ∂ 9.7 (s, 1H, O-**H**)

Compound (F'')

UV : Spectrum No. 4

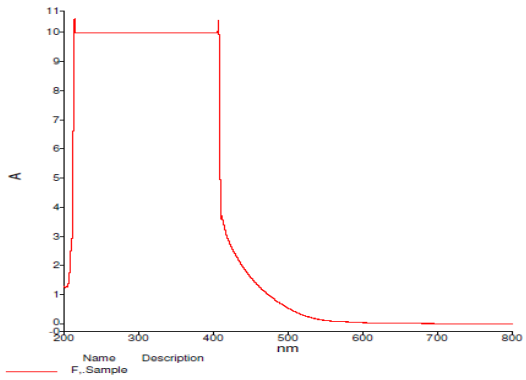
The UV-Vis spectrum of the compound F" reported in dioxane showed λ_{max} value 400 nm corresponding to n→π* transition.

IR (KBr): Spectrum No. 5

1648 cm^{-1} (=C=O stretching), 3429.3 cm^{-1} (-OH phenolic), 2925.7 cm^{-1} (aliphatic -C-H stretching), 3068.5 cm^{-1} (aromatic -C-H stretching), 1434 cm^{-1} (-C=N stretching), 1365.3 cm^{-1} [(C-N) (C-NO_2) stretching], 738.3 cm^{-1} (C-Cl stretching in aliphatic), 2547.12 cm^{-1} (-S-H stretching).

PMR: Spectrum No. 6

∂ 7.7 to 7.9 (m, 8H, Ar-**H**) ; ∂ 5.3 (s, 1H, O-**H**)



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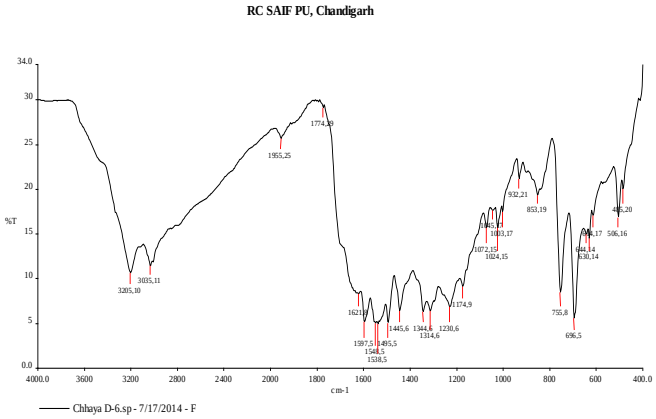

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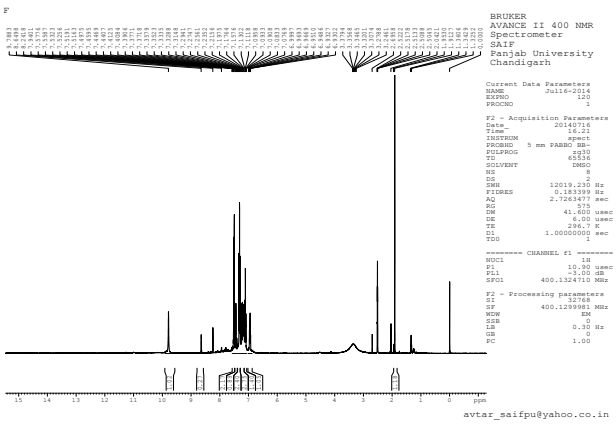

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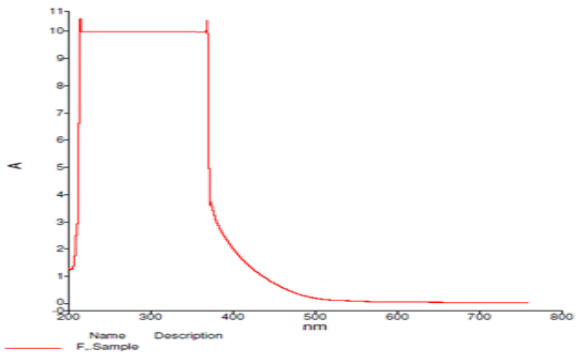

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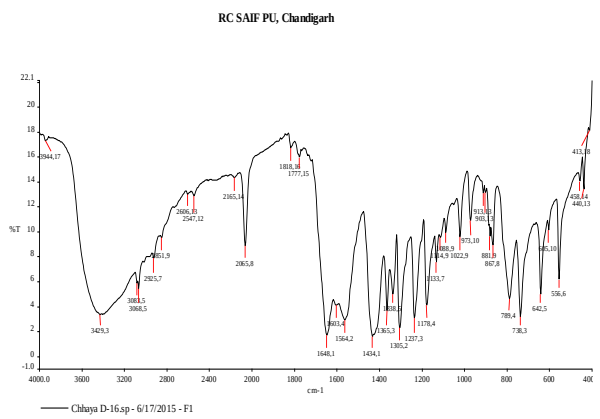

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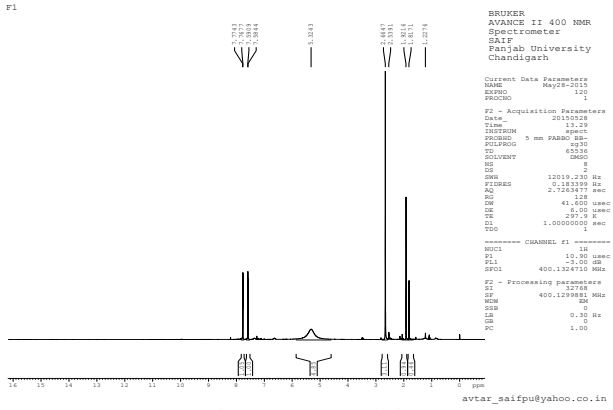
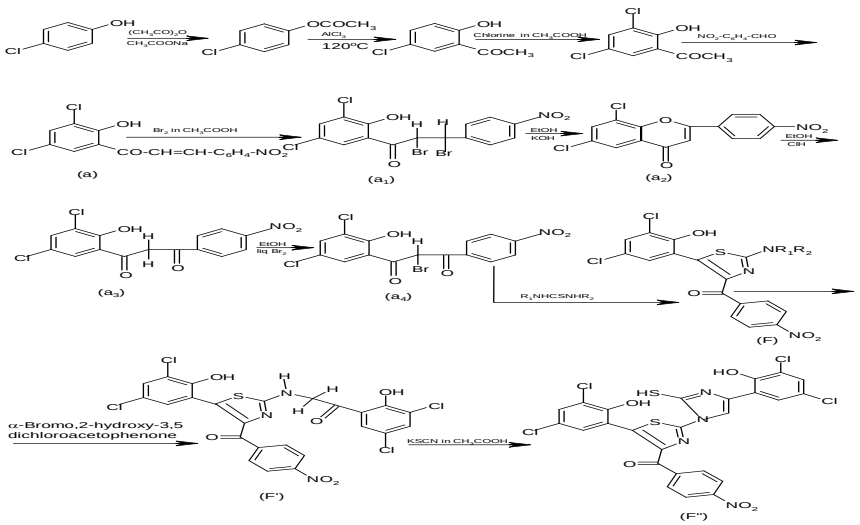


Spectrum No. 06

Table. 1: Characterisation data of newly synthesized compounds.

Compounds	Molecular formula	M.P. in ^{0}C	% 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
F	$C_{28}H_{17}O_4N_3Cl_2S$	180	75	59/59.78	3.00/3.02	7.40/7.47	5.60/5.69	12.60/12.63	
F’	$C_{30}H_{17}O_6N_3Cl_4S$	98	70	52.02/52.24	2.40/2.46	6.00/6.09	4.6/4.64	20.50/20.60	
F”	$C_{31}H_{18}O_5N_4Cl_4S_2$	132	70	50.72/50.80	2.42/2.45	7.62/7.65	8.67/8.74	19.27/19.39	



Scheme.

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

Experimental Details and Discussion of Results

The newly synthesized thiazoles, their imidazole derivatives (F, F’& F”) and their nanoparticles in the study were tested against some common pathogens for their antifungal and antibacterial activities, using disc diffusion method. The vegetable crop pathogens namely *Aspergillus niger, Pseudomonas lachrymans, Fusarium oxysporum, Fusarium solani* were procured from Department of Plant Pathology, Punjabrao Deshmukh Agriculture Krishi Vidyapeeth, Akola.

The punch discs of 6.25 mm diameter of whatman filter paper No. 1 were prepared and dispensed in the batches of 100 inch in screw capped bottles. These were sterilized by dry heat at 140^{o}C for 60 minutes. The solutions of 0.01 mole dilution of the nanoparticles of test compounds mentioned in the part V of the study

were prepared in dioxane solvent. The discs were soaked assuming that each discs will contain approximately 0.01 ml of the test solution.

The culture media for pathogens was prepared by using the following composition for one litre distilled water.

Composition of nutrient agar-agar

Peptone	: 5.0 g/litre
Sodium chloride	: 5.0 g/litre
Beef extract	: 1.5 g/litre
Yeast extract	: 1.5 g/litre
Agar	: 15.0 g/litre
pH (approximately)	: 7.4 + 0.2

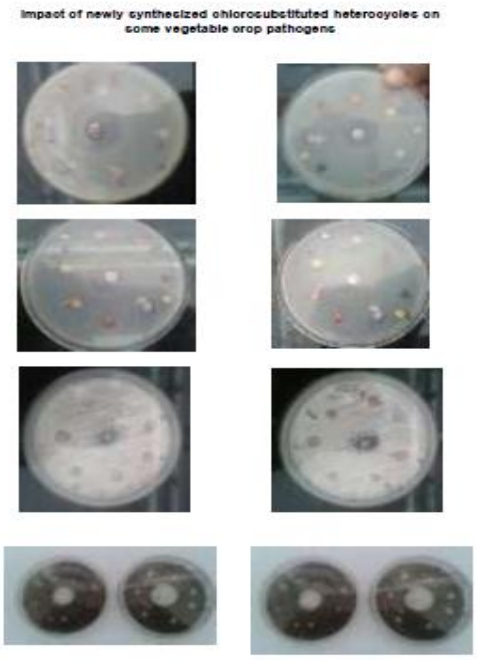
The culture medium prepared was sterilized in an autoclave at 15 lbs/inch pressure at 121^{o}C temperature for 15 minutes. After sterilization it was cooled down to about 50^{o}C and poured into presterilized petriplates of 8.5 cm in diameter each and allowed to solidify the nutrient agar medium of about 14 m depth. The petriplates were kept with nutrient broath at 37^{o}C for 4 hours in an incubator.

The cultures of pathogens were innoculated separately in petriplates on the surface nutrient agar broath uniformly with all a septic precautions. The plates were dried again for 30 minutes and without further delay the discs soaked in the test compounds were applied at adequate spacing 2 cm or more apart to the surface medium with the help of sterilized forceps. The discs were pressed gently to ensure their full contacts with the medium. The control was run using plane dioxane solvent for aseptic conditions. The plates were kept in incubator at 37^{o}C for about 18 to 24 hours. Soon after the incubation period is over the degree of sensitivity to test the compounds were determined by measuring the visible clear area of growth free zones [zone of inhibition] produced by diffusion of the antibiotics into media from the discs by calipers in mm. The results are tabulated as:

Zones of Inhibition (mm)
Vegetable Crop Pathogens
Zones of Inhibition (mm)
Vegetable Crop Pathogens

Sr. No.	Aspergillus niger	Pseudomonas lachrymans	Fusarium oxysporum	Fusarium solani
(1) F	1 mm	2 mm	1 mm	-
(2) F’	1.0 mm	2.0 mm	1.5 mm	2 mm
(3) F”	2.5 mm	2.5 mm	1.5 mm	2 mm
(4) Control	-	-	-	-
(5)Antibacterial agent	-	11 mm	11 mm	-
(6)Antifungal agent	8 mm	-	8 mm	-

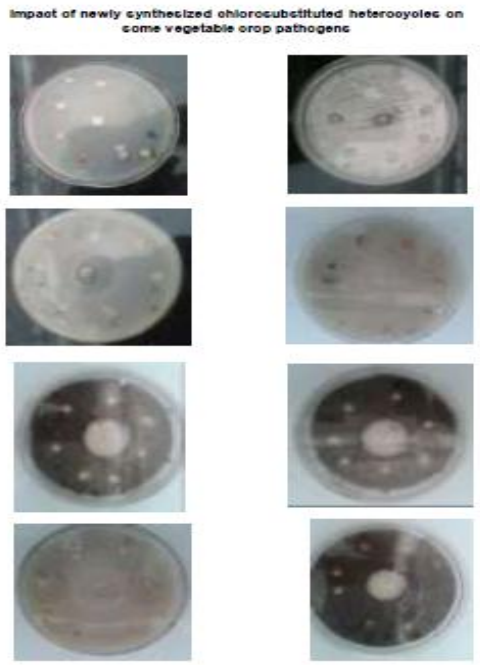
Zero mm	:	Non active
0 – 2 mm	:	Weakly active
3 – 5 mm	:	Moderately active
6 – 8 mm	:	Active
9 – 11 mm	:	Strongly active
12 – 14 mm	:	Very strongly active



RESULT AND DISCUSSION

The nanoparticles of test compounds when screened *in vitro* against test vegetable crop pathogens viz. *Aspergillus niger, Pseudomonas lachrymans, Fusarium oxysporum, Fusarium solani* then it was noticed that most of these compounds (F, F’ & F”) showed remarkable inhibitory activity against all the test organisms.

Compound F” shows remarkable inhibitory activity against vegetable crop pathogen *Aspergillus niger, Pseudomonas lachrymans, Fusarium solani.*



ACKNOWLEDGEMENTS

The authors are thankful to Dr.D.H.Pundkar, Principal, Dr.Manorama & Prof.H. S.Pundkar, Arts, Commerce & Science College, Balapur, Dr.B.B.Wankhade, Principal, Malkapur Vidnyan Mahavidyalaya, Malkapur, and Shri Shankarlal Khandelwal College, Akola for providing help in carrying out the antibacterial activities & for providing necessary facilities to carry out the research work.

REFERENCES

1. Chigarambatla Kistayya, N.G. Raghavendra Rao, B. Sanjeev Nayak, V.N. Sonar ; Journal of advanced Scientific Research ISSN 0976- 9595. 2231-606 X.
2. Kamal Dawood, Taha M.A., Eldebss Heba S.A., El-Zahabi, Mohmoud H. Yousef Peter Metz, European Journal of Medicinal Chemistry, 2013; 70" 740-749.
3. Tantry Rajesh N ; Jathi Keshavayya*, Prasanna S.M., Angadi Shoukat Ali R. and Chinnagiri Keerthi Kumar T., Research Journal of Chemical Sciences, Vol. 4 (1), 1-8, January 2014, ISSN.
4. Hamid Reza Jaberi and Hadi Noori Zadeh, ISSN : 0973-4945 CODEN ECJHAO E-Journel of Chemistry, 2012; 9(3): 1518-1525.
5. Karabasanagouda T., Airody Vasudeva Adhikari, Ramgopal Dhanwad and G. Parameshwarappa, Indian Journal of Chemistry vol. 47 B, January 2008; 144-152.
6. Javad Safaei Ghomi, Fariba Salimi and Ali Ramazani, J. Chem. Sci., Vol. 125, No. 5, September 2013; 1087-1092.
7. E.M. Sharshira, N.M.M. Hemada, American Journal of Organic chemistry, 2012; 2(3): 69-73-2012.
8. K. Anilkumar, P.K., K. Shrivastava Rao, Reddana P., Ind. J. of chem. sec., B., 1033-1037, June 2007.
9. Khare, P.K., H. Singh, Shrivastava, Indian J. Chem., Sec., B, May 2007; 875-879.
10. Pathan S.R., Dighe N. and S. Shinde, H.V. Asian J. of Research chem., April-June 2009; 2(2).
11. Rzaeva I.A., Sadigova S.E., Vekilova T.M., Acta Crysta., April 2007; 63: 1598-1600.
12. Chawlal Amit, Sheelmani, Arashdeep Singh, Chawla Payal, Dhawan R.K., Adv. J. Pharma life science Res., 2014; 2(1): 1-7.
13. G.R. Subbanwad, Y.B. Vibhute, Indian Chem. Soc., 1992, 69 (11), 781 -3 (Eng.): Chem. Abstr. 120 (1994), pp.no. 106850.
14. D.T. Witiar, M.E. Wolff and R.C. Covestri, "In Berger" S. Medicinal Chemistry" Part III, Ed.: (Wiley, New York) (1981), 605.
15. Koneni V. Sashidhara*, K. Bhaskara Rao[a], Vikas Kushwaha[b], Ram K. Madhukuri, Richa Verma, P.K. Murthy, European Journal of Medicinal Chemistry, 2014; 81: 473-80.
16. Ayman Khdair, Di Chen, Yogesh Patil, Linon Ma, Q. Ping Dou, Malathy P.V. Shekhar, Jayanth Panyom, Journal of Controlled Release, Volume 141, Issue 2, 25 January (2010). Pg.no. 137-144.
17. Dr. Ho, Nanotech advancements, Scientific hardness nanotechnology to better diagnose and tract cancer, 120: 2781-2783; doi 10.1002/Cner.28982.
18. Andrel L. Gartel, University of Illinois, USA/Pharmaceutica-(2013).
19. Chun-Mao Lin and Tan-Yi Lu, Bentham Science, ISSN : 2212-4020.