ISSN: 0975-833X

Available online at http://www.journalcra.com

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

International Journal of Current Research
Vol. 14, Issue, 02, pp.20572-20576, February, 2022

DOI: https://doi.org/10.24941/ijcr.43041.02.2022

RESEARCH ARTICLE

CONVENTIONAL SYNTHESIS AND STUDY OF ALKYL SUBSTITUTED 1,3-THIAZOLE AND ITS NANOPARTICLES WITH SPECIAL REFERENCE TO PLANT PATHOGENS OF SOME VEGETABLE CROPS

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ARTICLE INFO

Article History:
Received 27th November, 2021
Received in revised form
19th December, 2021
Accepted 24th January, 2022
Published online 25th February, 2022

Keywords:

Chalcone, Thiazole,
Phenyl Thiourea,
Antipathogenic Activities.

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ABSTRACT

The synthesis, spectral analysis and biological activities of 5-phenyl-2- hydroxy-chlorosubstituted-2-amino-1,3 thiazoles have been carried out. In this case 5- (2'-hydroxy-3',5'-dichlorophenyl)-4-(heptan-1-one)-2-phenyl amino-1,3-thiazole (K) has been screened. The compound K was synthesized from 1-(2'-hydroxy-3',5'- dichlorophenyl)-2-bromo-1,3-nonanedione (a4) by the action of phenylthiourea. The nanoparticles of the compound K has been prepared by using ultrasonic technique. The titled compound and its nanoparticles were assayed for antipathogenic impact against some common crop pathogens viz - *Aspergillus niger, Pseudomonas lachrymans, Fusarium oxysporum* and *Fusarium solani.*

Citation: Chhaya d. Badnakhe. "Conventional Synthesis And Study Of Alkyl Substituted 1,3- Thiazole And Its Nanoparticles With Special Reference To Plant Pathogens Of Some Vegetable Crops.", *2022. International Journal of Current Research, 14, (02), 20572-20576.*

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 called 1,3-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. 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]. Chalcones and their analogues having α, β-unsaturated carbonyl system are very versatile substrates for the evolution of various reactions and physiologically active compounds.

In the present study, various 5-phenyl-2-hydroxy-chlorosubstituted-2-amino- 1,3 thiazole has been synthesized from 1,3 propanediones by using phenyl thiourea. Nanotechnology has the potential to change the entire scenario of the current agricultural and food industry with the help of new tools developed for the treatment of plant diseases, rapid detection of pathogens using nanobased kits, improving the ability of plants to absorb nutrients etc. Nanobiosensors and other smart delivery systems will also help the agricultural industry to fight against different crop pathogens. 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 Breast & liver cancer[12], cancer & HIV[13], brain cancer[14], inhibiting tumour growth[15].Nanotechnology as the potential to revolutionize the different sectors of agriculture and food industry with modern tools for the treatment of diseases, rapid disease detection, enhancing the ability of plants to absorb nutrients by use of advanced technologies like nanocapsulation of elderberry extract using outer membrane of

living cells[16],cosmetic technology[17], vitro-dissolution[18], enhancing cell efficiency of photovoltaic cell[19] . In the present study, the chlorosubstituted 1,3-thiazole (K) has been prepared along with its 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 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.

Hydroxy 3',5'-dichloroacetophenone: 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'-dichlorophenyl-4-hexylchalcone (a): 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 (a).

Preparation of 1-(2'-hydroxy-3'-5'-dichlorophenyl)-2,3-dibromononan-1-one (a1) 2'-Hydroxy-3',5'-dichlorophenyl-4-hexylchalcone

a little petroleum ether to get the compound (**a1**).
Preparation of 2-(4"-hexyl)- 6,8-dichloroflavone (a2): 1-(2'-Hydroxy-3',5'-dichlorophenyl)-2,3-dibromo-nonan-1-one (a1) (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 (a2).

Preparation of 1-(2'-hydroxy-3',5'-dichlorophenyl)-1,3-nonanedione (a3): 2-(4"-Hexyl)-6,8-dichloroflavone (a2) (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 (a3).

Preparation of 1-(2'-hydroxy-3',5'-dichlorophenyl)-2-bromo-1,3-nonanedione (a4): 1-(2'-Hydroxy-3',5'-dichlorophenyl)-1,3-nonanedione (a3) (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 (a4).

Preparation of 5-(2'-hydroxy-3',5'-dichlorophenyl)-4-(heptan-1-one)-2-phenyl amino-1,3-thiazole (K): 1-(2'-Hydroxy-3',5'-dichlorophenyl)-2-bromo-1,3-nonanedione (a4) (0.01 mol) and phenylthiourea (0.01 mol) were dissolved in ethanol (25 ml). To this, aq. KOH solution (0.02 mol) was added. The reaction mixture was 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 (K). The newly synthesized compound was characterised on the basis of elemental analysis, molecular determination, UV, IR, NMR. spectral data.

The UV, IR, and NMR spectral data :- Compound (K):

UV: Spectrum No. 1

The UV-Vis spectrum of the compound (K) reported in dioxane showed λmax value 392 nm corresponding to $n \rightarrow \pi^*$ transition.

IR KBr : Spectrum No. 2

3078.56 cm^{-1} (O-H phenolic), 2956.24 cm^{-1} (aliphatic -C-H stretching) , 3305.55 cm^{-1} (aromatic C-H stretching) , 3786.79 cm^{-1} (-NH stretching), 1552.51 cm^{-1} (-C=N-stretching) , 754.50 cm^{-1} [C-Cl stretching in aliphatic) , 1174.48 cm^{-1} [C-Cl stretching in aromatic].

PMR:- Spectrum No. 3

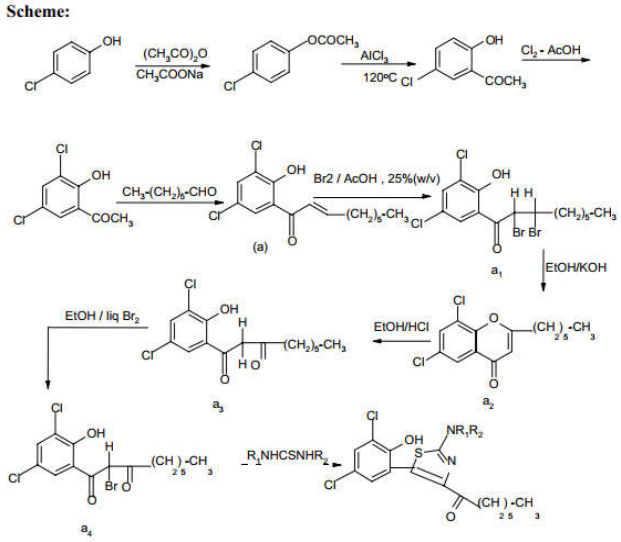
∂ 1.06 (t, 3H, -CH_2-C**H**$_3$); ∂ 1.25 [Envelope of –CH_2 , 8H, -(C**H**$_2$)**4**-CH_3], ∂ 3.32

(a) (0.01 M) was suspended in bromine–glacial acid reag
(hump, 2H, -N**H**) ; ∂ 4.15 (d 1H, -CH=C-**H**-) ; ∂ 4.16 (d, 1H, -C**H**=C-H-); ∂ 7.01 to 7.72 (m, 7H, Ar-**H**).

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 solution. This solution was taken in a beaker and the probe of the sonapras 250 MP was dipped in solution. This 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 introduced to the X-ray diffraction instrument to get graphical

information which was used for the calculation of the crystal size of test compounds.

Scheme:



Where :

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

Characterisation of size of nanoparticles of the test compounds: The crystal size of nanoparticles of the test compounds calculated by using Debye-Scherrer equation.

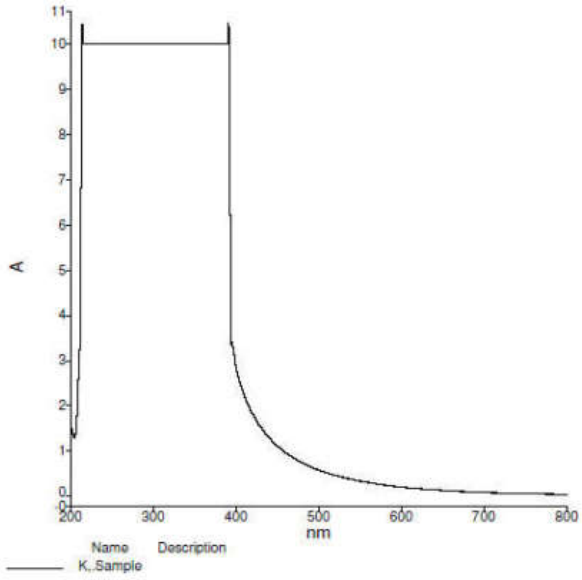
$$D = \frac{0.94\ \lambda}{\beta .\ \text{Cos}\ \theta}$$

Where,

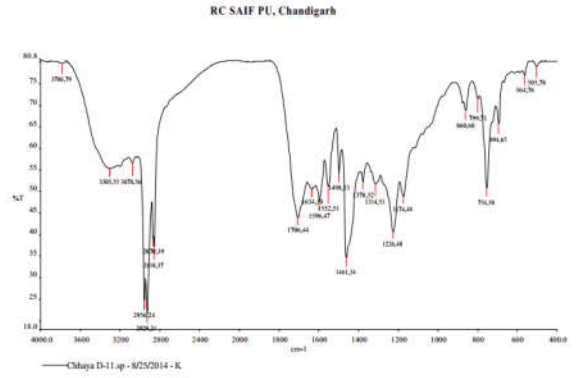
D = The average crystalline size.
0.94 = The particle shape factor which depends on the shape and size of the particle.
λ = is the wavelength.
β = is the full width at half maximum [FWHM] of the selected diffraction peaks (β = 0.545)
θ = is the Bragg's angle obtained from 2θ values which was corresponding to the maximum intensity peak in XRD pattern (θ = 0.7501 rad).

RESULTS AND DISCUSSION

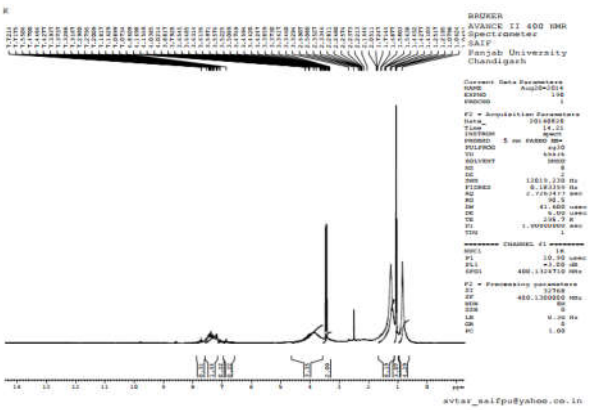
The newly synthesized thiazine (K) and its nanoparticles in the study were tested against some common pathogens for their antifungal and antibacterial activities, using disc diffusion method. The vegetable crop pathogens namely *Aspergillus niger, Pseudomonas lachrymans, Fusarium oxysporum, Fusarium 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°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.



Spectrum No. 1



Spectrum No. 2



Spectrum No. 3

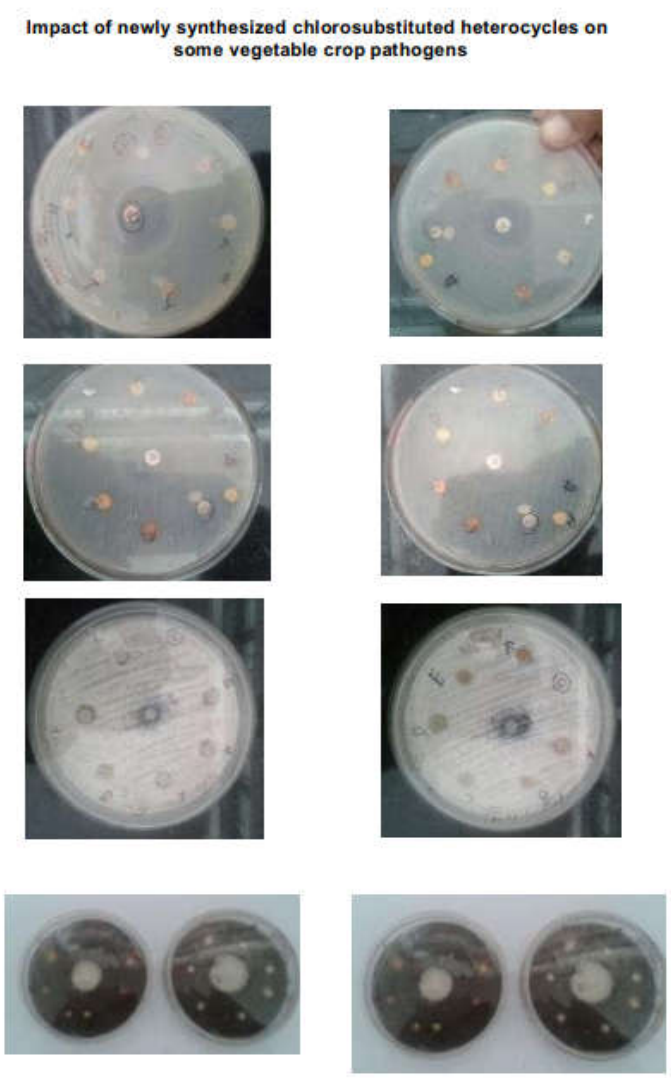
The culture media for pathogens was prepared by using the following composition for one litre distilled water.

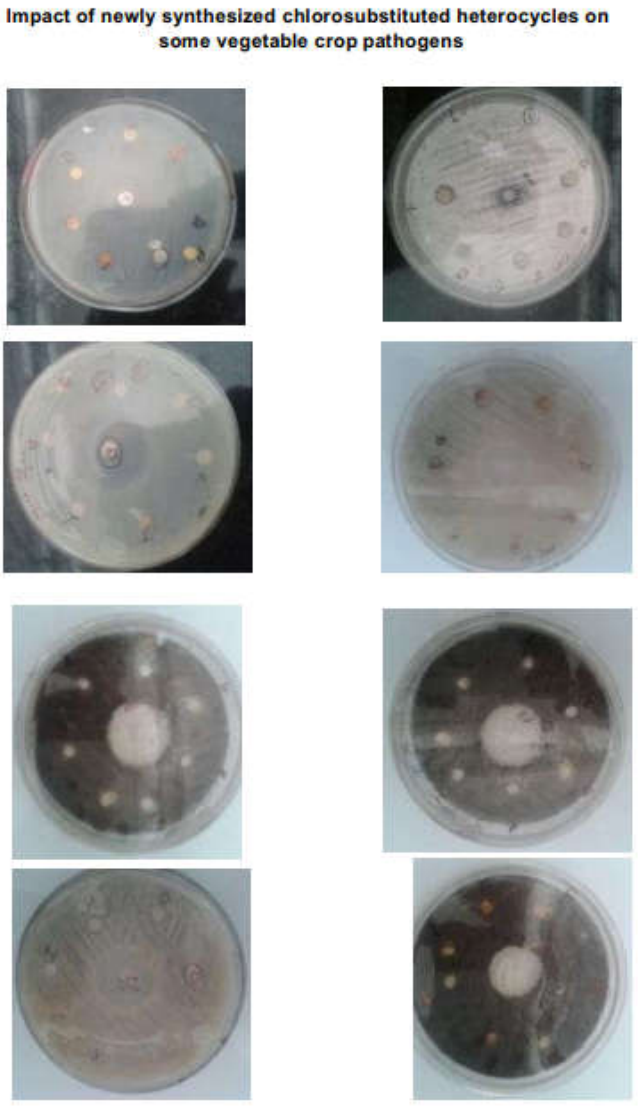
Composition of nutrient agar-agar

- 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

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	$C_{15}H_{18}O_2Cl_2$	103	70	52.20/53.35	53.10/53.21			23.25/23.27	
a1	$C_{15}H_{18}O_2Cl_2Br_2$	67	50	39.01/39.04	3.85/3.90			15.20/15.40	34.18/34.70
a2	$C_{15}H_{16}O_2Cl_2$	73	50	60.10/60.20	5.25/5.35			23.70/23.74	
a3	$C_{15}H_{18}O_3Cl_2$	118	60	56.60/56.78	5.60/5.67			22.33/22.39	
a4	$C_{15}H_{17}O_3Cl_2Br$	84	50	45.40/45.45	4.20/4.29			17.90/17.92	20.15/20.20
K	$C_{22}H_{23}O_2N_2Cl_2S$	135	60	58.46/58.66	5.07/5.11	6.18/6.22	7.00/7.11	15.60/15.77	





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

Sr.No.	Aspergillus niger	Pseudomonas lachrymans	Fusarium oxysporum	Fusarium solani
(1) K (9d)	-	-	1.5 mm	-
(2) Control	-	-	-	-
(3) Antibacterial agent	-	11 mm	11 mm	-
(4) 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 compound when screened *in vitro* against test vegetable crop pathogens viz. *Aspergillus niger, Pseudomonas lachrymans, Fusarium oxysporum, Fusarium solani* then it was noticed that the compound (K) showed remarkable inhibitory activity against *Fusarium oxysporum.*

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.

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