



UNIQUE SYNTHESIS AND STUDY OF SUBSTITUTED 1,3-THIAZINE AND ITS NANOPARTICLES AS ANTIBACTERIAL AGENTS

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ABSTRACT

The synthesis, spectral analysis and biological activities of 4-phenyl-2-hydroxy-chlorosubstituted-2-imino-1,3-thiazines have been carried out. In this case 4-(2'-hydroxy-3',5'-dichlorophenyl)-6-(hexyl)-2-imino-3,6-dihydro-1,3-thiazine (G) has been screened. The compound G was synthesized from 2'-hydroxy-3',5'-dichlorophenyl-4-(hexyl) chalcone (a'') by the action of thiourea. The compound (a'') was synthesized from 2'-hydroxy-3',5'-dichloroacetophenone by the action of heptanaldehyde in ethanol and 40% NaOH. The nanoparticles of the compounds G has 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, antibacterial assay.

INTRODUCTION

Thiazine is a six membered ring system, which contains two hetero atom [N and S] placed in the heterocyclic ring at 1, 3 positions. Many workers have synthesized different 1,3-thiazines.^[1-3] Thiazines are very useful units in the field of medicinal and pharmaceutical chemistry and have been reported to exhibit a variety of biological activities such as antiserotonin,^[4] antipsychotic,^[5] anti-HIV,^[6] antimicrobial,^[7] antiviral,^[8] blood platelet aggregation inhibitors^[9] and Ca⁺⁺ antagonist.^[10] Moreover thiazine nucleus is a pharmacophore of cephalosporin that occupy a very important place in the antibiotics and antifungal activity of thiazine nucleus is due to the presence of thiourea linkage in the structure. Chalcones and their analogues having α,β -unsaturated carbonyl system are very versatile substrates for the evolution of various reactions and physiologically active compounds. The reaction of thiourea with α,β -unsaturated ketones results in 1,3-thiazine. It has been well focused that the presence of 4-phenyl-chlorosubstituted moieties as well as 2-substituted amino group present in thiazine ring is an important structural

feature and the resulting molecule would exhibit promising biological activities.^[11-13]

In the present study, 4 -phenyl-2-substituted-imino-thiazine (G) has been synthesized from chalcones by using thiourea. The synthesized compound has been prepared along with its nanoparticles and screened them 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.

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 pellets, ¹H NMR spectra on spectrophotometer in CDCl₃ 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°C. The mixture was allowed to stand for 30 minutes. It was poured into 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'')

2'-Hydroxy-3',5'-dichloroacetophenone (0.1 mol) was dissolved in ethanol (50 ml) and heptaldehyde (0.1 mol) was added gradually to the above solution and the mixture was heated to boiling temperature. Aqueous sodium hydroxide solution [40%; 40 ml] was added dropwise with constant stirring. The mixture was stirred mechanically at room temperature for about half an hour and kept overnight. It was then acidified by hydrochloric acid solution (10%). The solid product separated, was filtered, and washed with sodium bicarbonate (10%) followed by water. The crude product was crystallized from ethanol acetic acid mixture (a'').

Preparation of 4-(2'-hydroxy-3',5'-dichlorophenyl)-6-(hexyl)-2-imino-3,6-dihydro-1,3-thiazine (G)

2'-Hydroxy-3',5'-dichlorophenyl-4-hexylchalcone (a'') (0.01 mol) and thiourea (0.02 mol) were dissolved in ethanol (25 ml). To this aqueous KOH solution (0.02 mol) was added. The reaction mixture was refluxed for three hours, cooled and diluted with water then acidified with 1:1 HCl. The product thus obtained was crystallized from ethanol to get the compound (G).

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 (G)

UV: Spectrum No. 1

The UV-Vis spectrum of the compound (G) reported in dioxane showed $\lambda_{\max}$ value 397 nm corresponding to $n \rightarrow \pi^*$ transition.

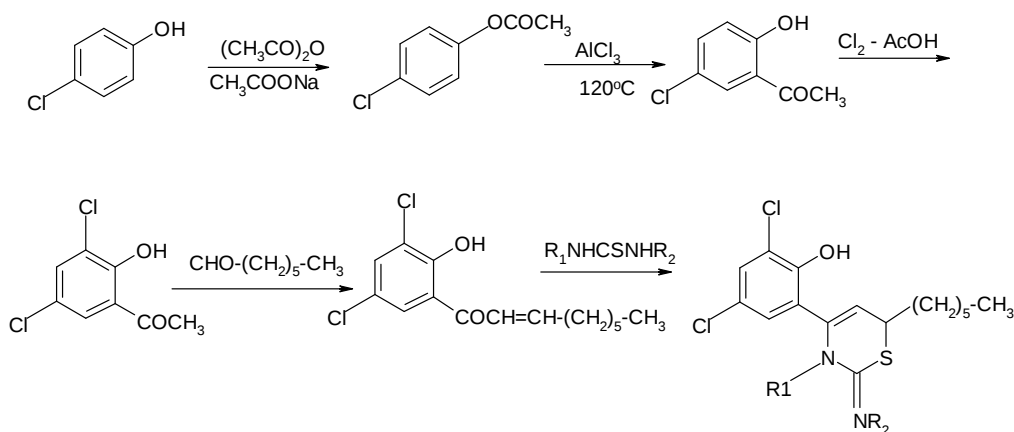
IR (KBr):- Spectrum No. 2

3208.63 cm^{-1} (-OH phenolic), 2928.36 cm^{-1} (aliphatic -C-H stretching), 2955.42 cm^{-1} (aromatic -C-H stretching), 3082.63 cm^{-1} (-N-H stretching), 1650.49 cm^{-1} (-C=N-stretching), 1023.73 cm^{-1} [(C-N) (C-NO₂) stretching], 740.62 cm^{-1} (-C-Cl stretching in aliphatic), 1177.7 cm^{-1} (C-Cl) stretching in aromatic).

PMR:- Spectrum No. 3

δ 1.25 (envelope of -CH₂, 10H, -(CH₂)₅-CH₃); δ 1.8 (d, 1H, -C=C-C-H); δ 3.5 (hump, 1H, =N-H); δ 6.7 (s, 1H, =N-H); δ 6.8 (d, 1H, =C-H); δ 7.0 to 7.8 (m, 2H, Ar-H); δ 12.36 (s, 1H, O-H)

Scheme



Where

- 1) R₁ = -H
- 2) R₂ = -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 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 introduced 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.

b = is the full width at half maximum [FWHM] of the selected diffraction peaks ($\beta = 0.545$)

q = is the Bragg's angle obtained from 2θ values which was corresponding to the maximum intensity peak in XRD pattern ($q = 0.7501$ rad).

EXPERIMENTAL DETAILS AND DISCUSSION OF RESULTS

Antibacterial Assay

All the newly synthesised compound (a-G) and it's nanoparticles 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.

The zones of inhibition formed were measured in mm and are shown in table -2.

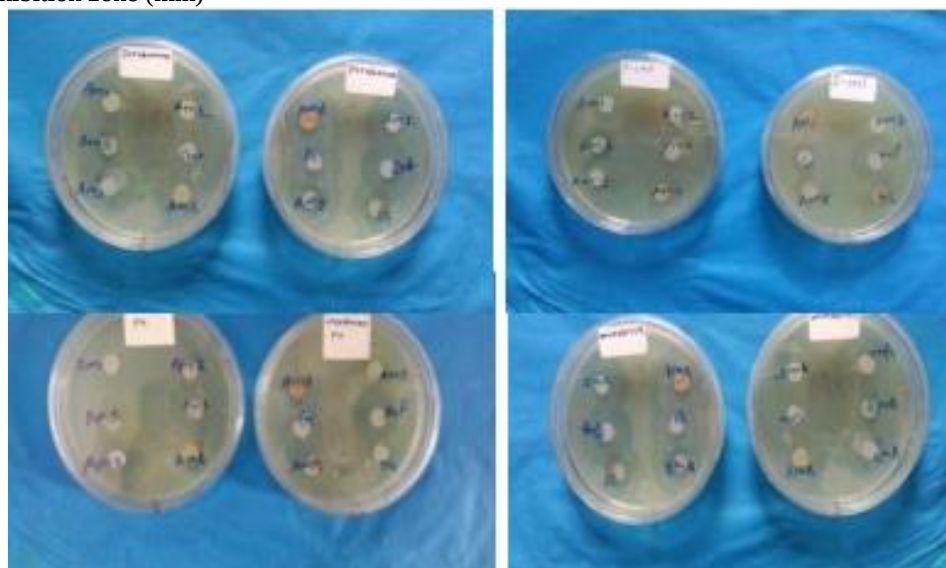
Table 1: Characterisation data of newly synthesized compounds.

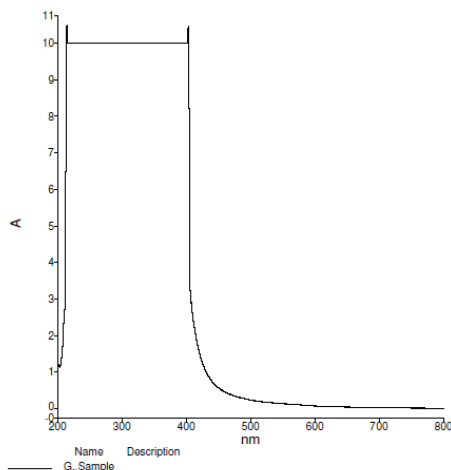
Compounds	Molecular formula	M.P. in °C	% of yield	% of element			
				C	H	N	S
a	C ₈ H ₆ O ₂ Cl ₂	54	80	47.90/48	2.95/3		
a''	C ₁₅ H ₁₈ O ₂ Cl ₂	103	70	59.80/59.25	53.10/60.26		
G	C ₁₆ H ₁₉ ON ₂ Cl ₂ S	178	70	58.63/58.12	5.30/5.12	7.82/7.90	8.93/8.70

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	11	15	12	12
a''	12	15	11	14
G	15	13	15	12
Reference Antibiotic	(Ofloxacin)	(Ofloxacin)	(Ofloxacin)	(Ofloxacin)

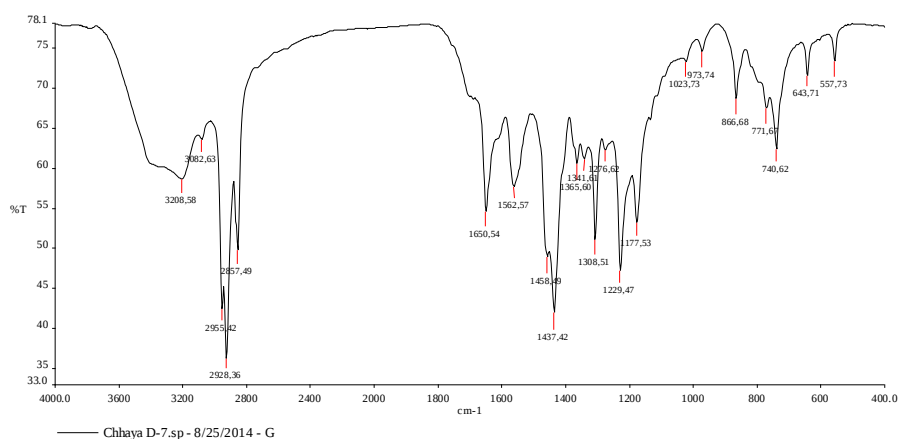
Diameter of inhibition zone (mm)



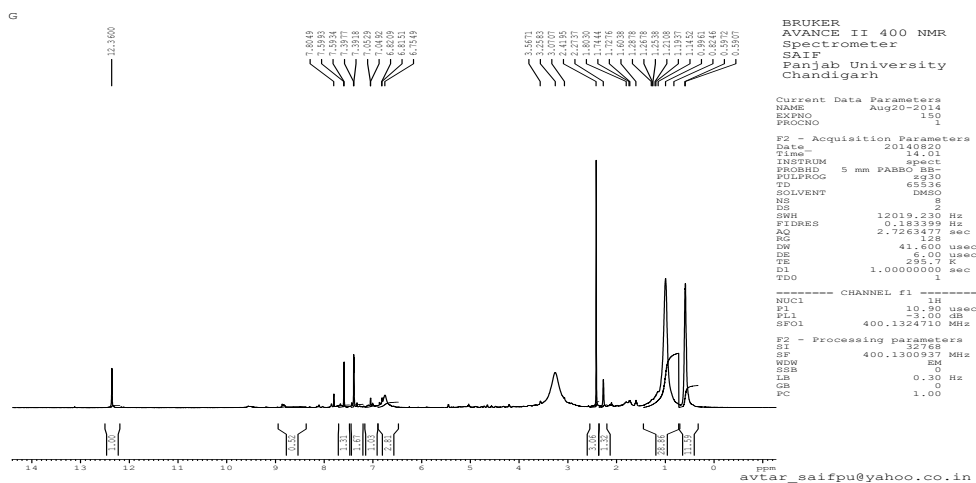


Spectrum No. 1.

RC SAIF PU, Chandigarh



Spectrum No. 2.



Spectrum No. 3.

RESULT AND DISCUSSION

The newly synthesized compound (a - G) and its nanoparticles were found to be active against test pathogens. However a further detailed study in the light of Medical sciences is advised.

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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