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Synthesis and Antibacterial Assay of some Substituted 1,3-Thiazines

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Abstract
The synthesis, spectral analysis and biological activities of 4-phenyl-2-hydroxy-chlorosubstituted-2-imino-1,3 thiazine has been reported. Compound ***A*** *(4-(2'-hydroxy-3',5'-dichlorophenyl)-6-(4''-nitrophenyl)-2-imino-3,6-dihydro-1,3- thiazine) was screened. Compound A was synthesized from 2'-hydroxy-3,5-dichlorophenyl-4-(4''-nitrophenyl) chalcone* ***(a)*** *by the action of thiourea. The compound* ***(a)*** *was synthesized from 2'-hydroxy-3',5'-dichloroacetophenone by the action of p-nitrobenzaldehyde in ethanol and 40% NaOH. The nanoparticles of the compounds* ***A*** *have been prepared by using ultrasonic technique. The newly synthesized titled compound and it's nanoparticles were screened for their antibacterial activities against Gram positive* Staphylococcus aureus *and* Streptococcus sp. *and Gram negative* Pseudomonas sp. *and* Solmonella typhi pathogens*. 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 atoms [N and S] placed in a heterocyclic ring at 1, 3 positions. Many workers have synthesized different 1,3-thiazines. Researchers have also reported the synthesis of several thiazines[1-6] and also their potent biological activities such as blood

platelet aggregation inhibition[7], antibacterial[8-9] antiallergic[10], anticholesterenic[11] and antifungal activities[12]. The thiazine nucleus is a pharmacophore of cephalosporin that occupies a very important place in the field of antibiotics and drug chemistry. Chalcones and their analogues having α, β-unsaturated carbonyl system are very versatile substrates for various reactions and physiologically active compounds. The reaction of thiourea with α, β-unsaturated ketones also results in the formation of 1,3-thiazines.The chlorosubstituted thiazines with amino group at position 2 in the ring exhibit promising biological activities[13-16].

In the present study, chlorosubstituted 1,3-thiazines (A) have been prepared along with their nanoparticles and were screened for their antibacterial activities against some Gram positive *Staphylococcus aureus* and *Streptococcus sp.* and Gram negative *Pseudomonas sp.* and *Solmonella typhi* pathogens. All the newly synthesized compounds were found to be active against test pathogens.

Materials and Methods

All the glassware 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 plates. IR spectra were recorded on Perkin-Elmer spectrophotometer using KBr pellets, H^1 NMR spectra were recorded on spectrophotometer in $CDCl_3$ with TMS as internal standard. UV spectra were recorded in nujol medium. 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 shown in Table 1.

Table 1 : Characterisation data of newly synthesized compounds

Compounds	Molecular formula	M.P. in ^{0}C	% of yield	% of element			
				C	H	N	S
p	$C_8H_6O_2Cl_2$	54	80	47.90/48.00	2.95/3.00		
a	$C_{15}H_9O_4NCl_2$	250	70	53.10/53.25	2.40/2.66	3.98/4.18	
A	$C_{16}H_{11}O_3N_3Cl_2S$	120	70	48.50/48.60	2.35/2.53	10.40/10.63	8.00/8.10

Preparation of 2'-Hydroxy 3',5'-dichloroacetophenone (*p*) :

2'-Hydroxy-5-chloroacetophenone (3g) was dissolved in acetic acid (5 mL), and mixed with sodium acetate (3g). To this reaction mixture, 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^{o}C. The mixture was allowed to stand for 30 minutes and then poured into water. A pale yellow solid thus obtained was filtered, dried and crystallized from ethanol to yield the compound.

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

2'-Hydroxy-3',5'-dichloroacetophenone (0.1 mol) was dissolved in ethanol (50 mL) and p-nitrobenzaldehyde (0.1 mol) was added gradually to the solution and the mixture was heated to boiling. Then aquous 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 for overnight. It was then acidified using hydrochloric acid (10%) solution. The solid product thus separated, was filtered, and washed with sodium bicarbonate (10%) followed by water. Finally

it was crystallized from ethanol acetic acid mixture to get the compound **(a)**.

Preparation of 4-(2'-hydroxy-3',5'-dichlorophenyl)-6-(4"-nitrophenyl)-2-imino-3,6-dihydro-1,3-thiazine (A) :

2'-Hydroxy-3,5-dichlorophenyl-4-(4"-nitrophenyl)-chalcone (a) (0.01 mol) and thiourea (0.02 mol) were dissolved in ethanol (30 mL). Aquous KOH solution (0.02 mol) was then added. The reaction mixture was refluxed for three hours, cooled and diluted with water and then acidified with 1:1 HCl. The product thus obtained was crystallized from ethanol to get the compound **(A)**.

The newly synthesized compounds were characterised on the basis of elemental analysis, molecular weight determination, UV, IR, NMR. spectral data.

UV, IR, and NMR spectral data:-

Compound (A):

UV: Spectrum No. 1

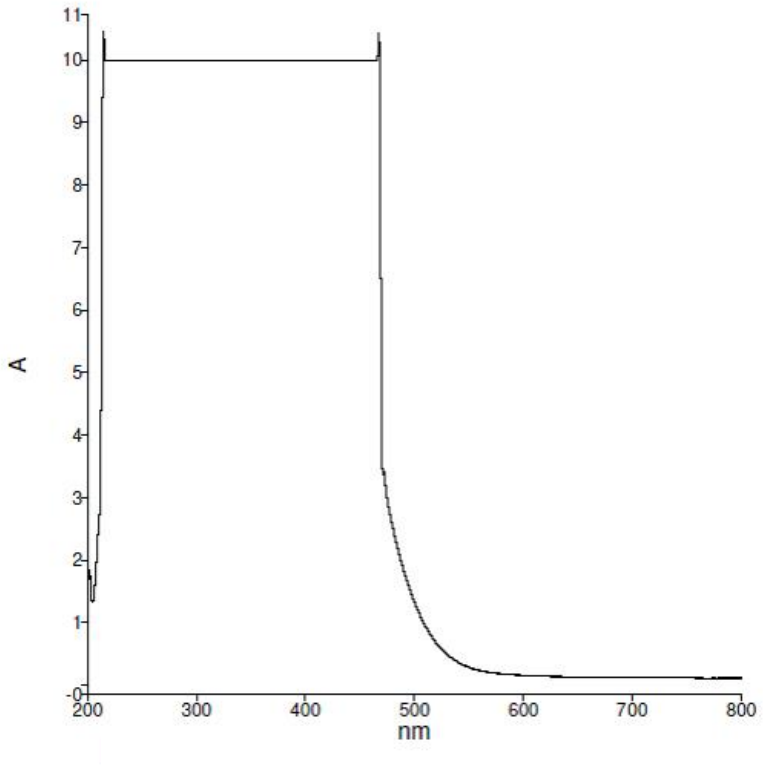
The UV-Vis spectrum of the compound **A** reported in dioxane showed λ_{max} value 495 nm corresponding to $n \rightarrow \pi^*$ transition.

IR (KBr):- Spectrum No. 2

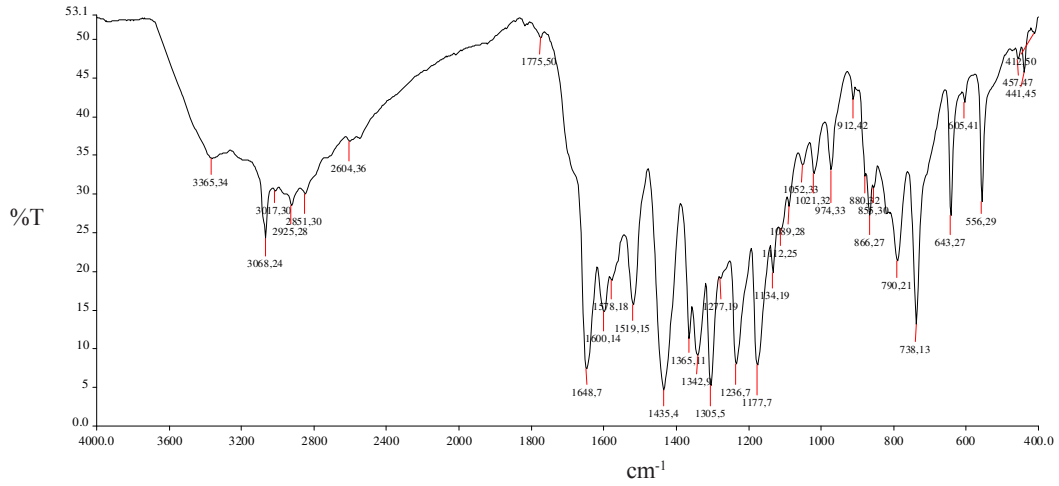
3365.34 cm^{-1} (-OH phenolic), 2925.2cm^{-1} (aliphatic -C-H stretching), 3068.24cm^{-1} (aromatic -C-H stretching), 3017.30 cm^{-1} (-N-H stretching), 1648.7 cm^{-1} (-C=N stretching), 1342 cm^{-1} [(C-N) (C-NO_2) stretching], 738.13 cm^{-1} (C-Cl stretching in aliphatic), 1177.7 cm^{-1} (C-Cl) stretching in aromatic).

PMR:- Spectrum No. 3

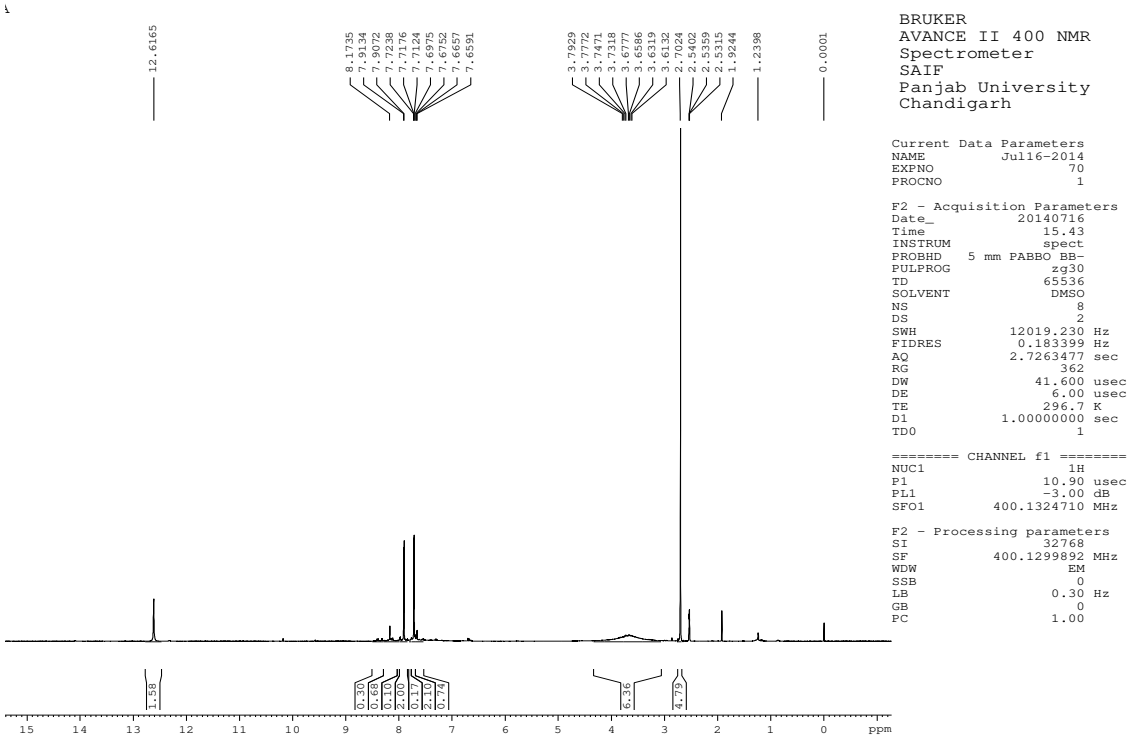
δ 1.2 (s, 1H, -C-H) ; δ 2.7 (s, 1H, =N -H) ; δ 3.6 (s, 1H, =N-H) ; δ 3.7 (s, 1H, = C-H) ; δ 7.6 to 8.1 (m, 6H, Ar-H) ; δ 12.6 (s, 1H, O-H)



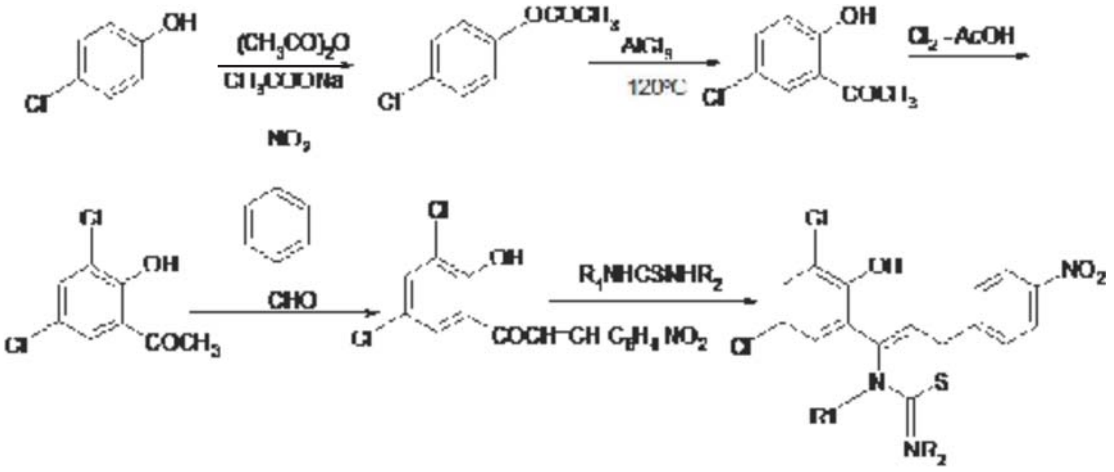
Spectrum No. 1



Spectrum No. 02



Spectrum No. 03



where 1) R_1 = -H
2) R_2 = -H

The newly synthesised compound **(A)** and its nanoparticles were screened for their antibacterial activity against some Gram positive pathogens viz. *Staphylococcus aureus* and *Streptococcus sp.* and some Gram negative pathogens viz. *Pseudomonas sp.* and *Solmonella Typhi.* at 1000 µm using Gentamycine as a standard. DMF was used as solvent control in agar plate technique. The zones of inhibition formed were measured in mm and are shown in Table 2.

Table 2: Antibacterial Activities of Synthesised New Compounds

Zones of inhibition (mm)

Compounds	*Staphylococcus aureus*	*Streptococcus sp.*	*Pseudomonas sp.*	*Solmonella typhi*
A	14	12	14	14
Nanoparticles of **A**	14	14	15	15

Results and Discussion

The newly synthesized compound **(A)** and its nanoparticles were found to be active against test pathogens. However a further detailed study in the light of medical science is required.

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