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SYNTHESIS AND ANTIBACTERIAL ASSAY OF NANOPARTICLES OF 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 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 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.

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 antiserotinin[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 has been synthesized from chalcones by using thiourea.

In the present study, the chlorosubstituted 1,3-thiazine (G) has been prepared along with it's 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.

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 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 heptnaldehyde (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 aquous 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).

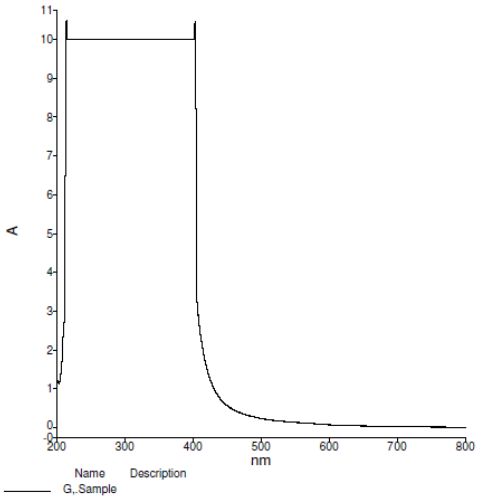
The newly synthesized compound was characterised on the basis of elemental analysis, molecular determination, UV, IR, NMR. spectral data.

The UV, IR, and NMR spectral data:-

Compound (G):

UV : Spectrum No. 1

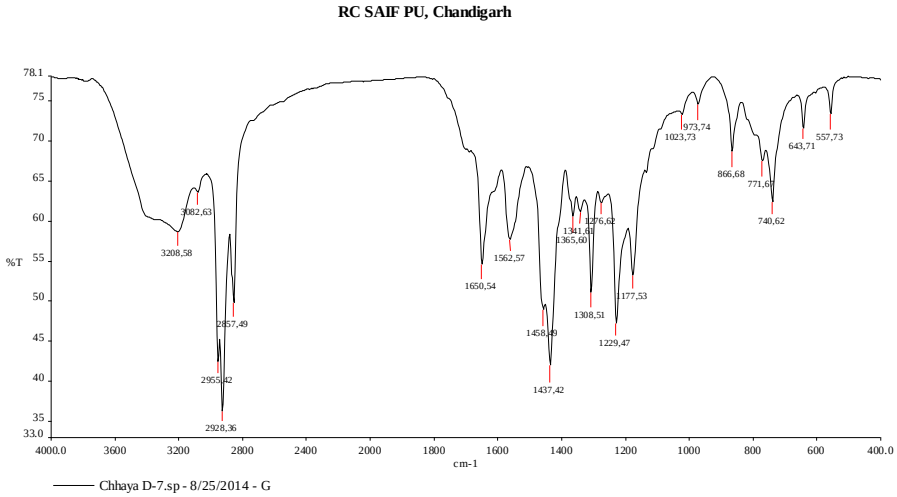
The UV-Vis spectrum of the compound (G) reported in dioxane showed λ_{max} value 397 nm corresponding to $n \rightarrow \pi^*$ transition.



Spectrum No. 1

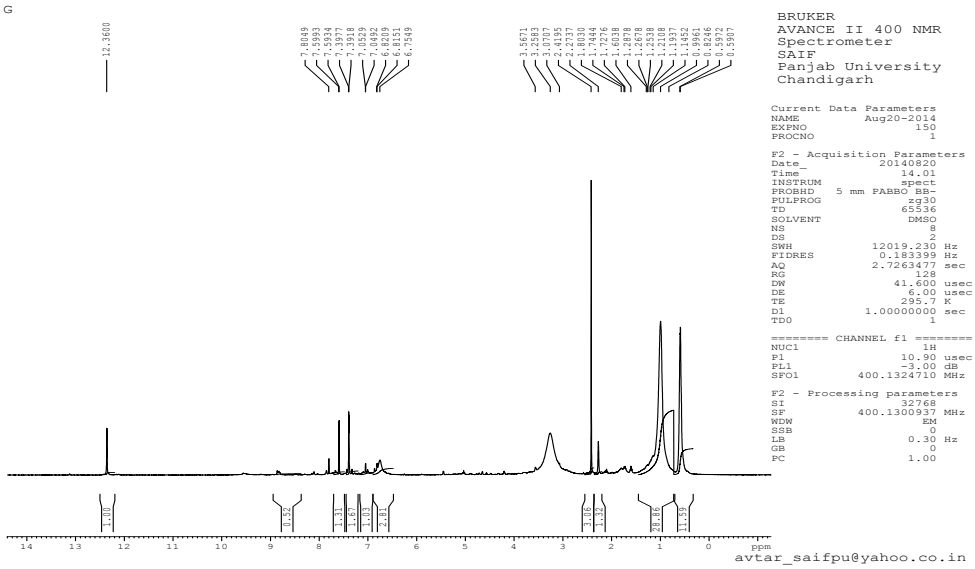
IR (KBr) :- Spectrum No. 2

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-NO_2) stretching], 740.62 cm^{-1} (-C-Cl stretching in aliphatic), 1177.7 cm^{-1} (C-Cl) stretching in aromatic).



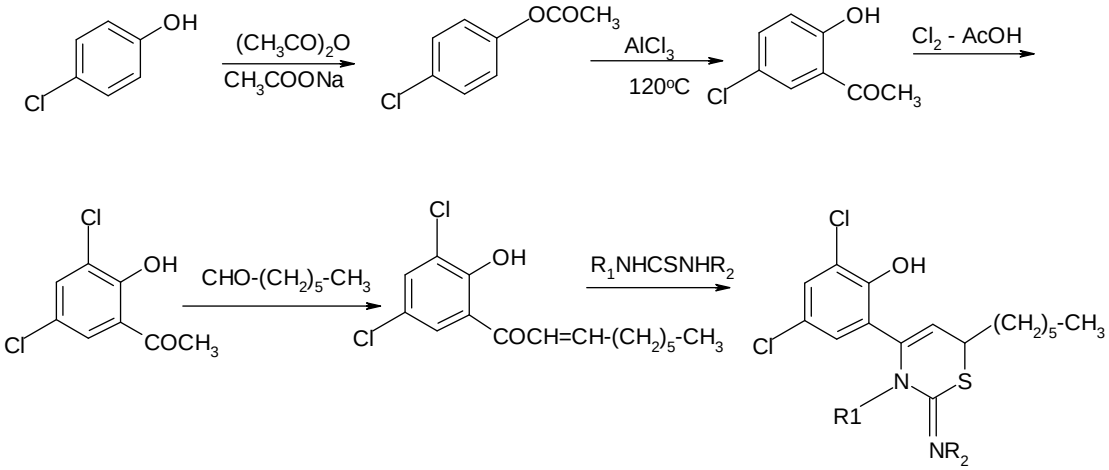
Spectrum No. 2

PMR :- Spectrum No. 3
∂ 1.25 (envelope of -CH_2, 10H, -$(CH_2)_5$-CH_3) ; ∂ 1.8 (d, 1H, -C=C-C-**H**) ; ∂ 3.5 (hump, 1H, =N-**H**) ; ∂ 6.7 (s, 1H, =N-**H**), ∂ 6.8 (d, 1H, =C-**H**) ; ∂ 7.0 to 7.8 (m, 2H, Ar-**H**) ; ∂ 12.36 (s, 1H, O-**H**)



Spectrum No. 3

Scheme:



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

All the newly synthesized compound (G) and it's 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 conc. of 1000 µm gentamycine as a standard. DMF was used as solvent control using agar plate techniques. The zones of inhibition formed were measured in mm and are shown in table -1.

TABLE-1
ANTIBACTERIAL ACTIVITIES OF SYNTHESISED NEW COMPOUNDS:

Zones of inhibition (mm)				
Compounds	**Staphylococcus aureus**	**Streptococcus sp.**	**Pseudomonas sp.**	**Solmonella typhi**
a	14	12	14	14
G	14	15	15	14

Table 2: Characterisation data of newly synthesized compounds:

Compounds	Molecular formula	M.P. in ^{0}C	% of yield	% of element			
				C	H	N	S
	$C_8H_6O_2Cl_2$	54	80	47.90/48	2.95/3		
a"	$C_{15}H_{18}O_2Cl_2$	103	70	59.80/59.25	53.10/60.26		
G	$C_{16}H_{19}ON_2Cl_2S$	178	70	58.63/58.12	5.30/5.12	7.82/7.90	8.93/8.70

RESULT AND DISCUSSION:

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

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