Eco friendly synthesis, characterization and antifungal study of chlorosubstituted thiazines

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Abstract: Literature survey reveals that 1,3 thiazine nucleus containing derivatives have a broad spectrum of biological as well as physiological activities.In the present segment of study some new chlorosubstituted 1,3 thiazines have been synthesized by condensation of 2 -hydroxy 3,5 dichloro 4 phenyl chalcone with thiourea and phenyl thiourea in ethanol containing aqueous KOH solution. The structures of newly synthesized chlorosubstituted thiazines have been elucidated on the basis of molecular weight determination, elemental analysis and spectral data. The newly synthesized chlorosubstituted 1,3 thiazines were prepared from chalcone and screened for their antifungal activity against *Aspergillus niger,Candida albicans,Pencillium chrysogenum and Tricoderma viridae* using agar diffusion method .

***Keywords**: Chlorosubstituted 1, 3 thiazines, Chalcone, Antifungal activity.*

Introduction:

Heterocyclic nucleus plays an important role in medicinal chemistry and it is a key template for the growth of various therapeutic agents.In organic chemistry a series of heterocyclic compounds containing an unsaturated six membered ring which contain two carbons, one nitrogen and one sulphur atom are termed as thiazines. Various methods have been worked out for their synthesis[1-7]. Derivatives of thiazines played a crucial role in the history of heterocyclic chemistry. Thiazine is the important class of heterocyclic compounds being studied by many researchers and possesses a wide variety of biological properties such as antiviral[8], antimicrobial[9], anti HIV[10], antiserotinin[11], antibacterial[12], antifungal[13].The studies also reveal that they can also be used as pesticides[14] and herbicides[15]. Numerous chlorinated compounds have various bioactivities which render them valuable active ingredients of medicine or plant protecting agents. Taking into consideration the widespread use of chlorosubstituted thiazines, it appears worthwhile to synthesize some new chlorosubstituted thiazines. The newly synthesized chlorosubstituted thiazines scheme 1 were assayed for their antifungal activity against some fungi i.e *Aspergillus niger,Candida albicans,Pencillium chrysogenum and Tricoderma viridae* using agar diffusion method .

Experimental:

The present study deals with the synthesis of chlorosubstituted 1,3-thiazines from chalcone on reaction with thiourea and phenylthiourea in alcoholic aqueous KOH medium .All the synthesized compounds were characterized on the basis of their chemical properties ,elemental analysis and spectral data .The melting points were determined by Thiel's apparatus by using capillary tubes. The purity of the compound was tested by TLC.IR spectra scanned on FTIR spectrophotometer in KBr pellets. H^1 NMR spectra in $CDCl_3$ were recorded.

Synthesis of 2-hydroxy- 3,5- dichloroacetophenone (3a)

2-Hydroxy -5 dichloroacetophenone (3g) was dissolved in acetic acid (5ml), sodium acetate (3g) was added to the reaction mixture and then chlorine in acetic acid reagent (40ml) was added drop wise with constant stirring. Allowed stand for half an hour then it was poured into cold water. A pale yellow solid product thus separated was filtered and crystallize from ethanol to get the compound (3a).

Synthesis of 2-hydroxy -3,5 dichloro- 4-phenyl chalcones (4a)

2-Hydroxy 3,5 dichloroacetophenone (3a), (0.1M) was dissolved in ethanol (50ml), salicaldehyde (0.1M) was added to this solution and mixture was heated to boiling. Aqueous sodium hydroxide solution (40%) (40 ml) was added dropwise with constant stirring. The mixture was shaken for half an hour, the product thus obtained then filtered, washed with sodium bicarbonate (10%) and purified by recrystallisation with ethanol to get 2-hydroxy 3,5 dichloro- 4- phenol chalcone (4a).

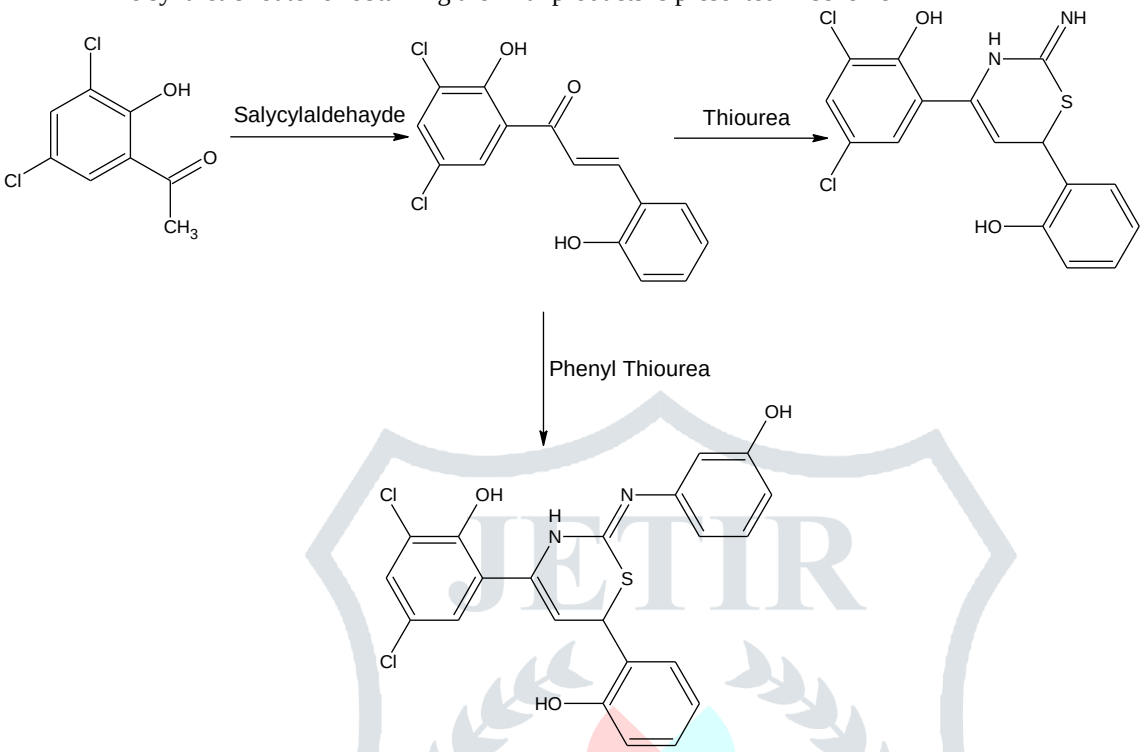
Synthesis of 4-(2-hydroxy 3,5 dichlorophenyl)-6-phenol-2- imino-3,6- dihydro-1,3 thiazine (5a)

2-Hydroxy 3,5 dichloro 4-phenyl chalcone (4a) (0.01 mol) and thiourea (0.01 mol) were dissolved in ethanol (25 ml), an aqueous potassium hydroxide solution (0.02 mol) was added. The reaction mixture was refluxed for 2.5hours. The reaction mixture was acidified with concentrated HCl. The product thus separated was crystallized from ethanol to get the compound 4-(2-hydroxy 3,5 dichlorophenyl)-6-phenol-2-imino-3,6 dihydro-1,3 thiazine (5a)

Synthesis of 4-(2-hydroxy 3,5 dichlorophenyl)-6-phenol-2-iminophenyl-3,6-dihydro 1,3-thiazine (6a)

2-Hydroxy 3,5 dichloro 4-phenyl chalcone (4a) (0.01 mol) and phenylthiourea (0.01 mol) were dissolved in ethanol (25 ml). To this solution an aqueous potassium hydroxide (0.02 mol) was added. The reaction mixture was refluxed for 2.5 hrs. After cooling it was acidified with concentrated HCl. Finally the product was crystallized from ethanol to get the compound 4-(2-hydroxy 3,5 dichlorophenyl)- 6-phenol- 2-iminophenyl -3,6-dihydro 1,3 thiazine (6a).

The synthetic route for obtaining the final products is presented in scheme 1



Scheme 1

Characterization:

Melting points of all synthesized compounds were determined in open capillaries and are uncorrected. IR spectra were recorded in KBr. The H^1 NMR spectra were recorded using TMS as internal standard and chemical shifts were expressed in δ (ppm) .

Table No. 1: Physical and analytical characterization data of newly synthesized compounds

Compounds	Mol. Formula	Mol. Wt	Yield%	Melting Point ^0C	Found Calculated %			
					C	H	Cl	N
3a	$C_8H_6Cl_2O_2$	205.03	80	53	45.55 (46.86)	2.90 (2.95)	33.90 (34.58)	-
4a	$C_{15}H_{10}Cl_2O_3$	309.14	75	120	57.12 (58.28)	3.10 (3.26)	21.35 (22.44)	-
5a	$C_{16}H_{12}Cl_2N_2O_2S$	167.25	60	110	50.15 (52.33)	2.90 (3.29)	18.54 (19.31)	6.50 (7.63)
6a	$C_{22}H_{16}Cl_2N_2O_3S$	459.34	65	115	56.82 (57.52)	2.85 (3.51)	14.42 (15.44)	5.32 (6.10)

Spectral study of 4-(2-hydroxy 3,5 dichlorophenyl)-6-phenol- 2-imino-3,6-dihydro-1,3 thiazine (5a)and 4-(2-hydroxy 3,5 dichlorophenyl)- 6-phenol-2-iminophenyl -3,6-dihydro-1,3 thiazine (6a) are summarized as

IR (KBr cm-1) of 5a : 3663 (O-H bending), 3500 (-NH stretching), 3085 (Ph stretching), 2980 (C-H stretching), 1654 (-C=N stretching), 1440 (-CH_2 bending), 1345 (-CH_3 bending), 1050 (C-S stretching), 1314 (-OH bending in Ph.), 698 (C-Cl stretching).

^{1}HNMR ($CDCl_3$) of 5a : δ 2.75 (s, 1H, -NH), δ 7.4 to 7.6 (m, 5H, ArH), δ 7.8 to 8.1 (s, 2H, ArH), δ 4.9 (s, 1H, N-Ph), δ 13.01 (s, 1H, ArOH).

IR (KBr cm-1) of 6a : 3665 (O-H bending), 3528 (-NH stretching), 3094 (Ph stretching), 2990 (C-H stretching), 1660 (-C=N stretching), 1445(-CH_2 bending), 1350 (-CH_3 bending), 1320 (-OH bending in Ph), 1065 (C-S stretching), 718 (C-Cl stretching).

H^{1}NMR ($CDCl_3$) of 6a : δ 2.79 (s, 1H, -NH), δ 7.5 to 7.7 (m, 5H, ArH), δ 7.9 to 8.3 (s, 2H, ArH), δ 5.1 (s, 1H, N-Ph), δ 13.20 (s, 1H, ArOH).

Result and Discussion:

The synthesized compounds were screened for their antifungal activity against some fungi i.e *Aspergillus niger,Candida albicans,Pencillium chrysogenum and Tricoderma viridae* using agar diffusion method . The compounds 5a and 6a shows activity against all the tested fungi.

Conclusion:

The newly synthesized chlorosubstituted 1,3 thiazines were characterized for their structure determination. Various chemical and spectral data supported the structures. Antifungal activities of 1,3-thiazines were screened against various fungal species and it is concluded that the compounds 5a and 6a showed significant activity against the tested species above 500ug.

Acknowledgement:

Authors are thankful to Principal and Head, Deptt. Of Chemistry, VBMV Amravati for providing laboratory facilities, Biogenic Research and Training Center in Biotechnology, Hubli ,Karnataka for providing microbial data and to the Director SAIF, Chandigarh for providing spectral data of the compounds.

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