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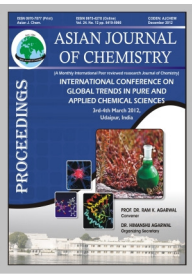

Synthesis and Antibacterial Studies of Chloro-Substituted 1,3-Thiazines†

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Thiazines are very useful units in the fields of medicinal and pharmaceutical chemistry and have been reported to exhibit a variety of biological activities. This has directed us to synthesize chloro-substituted thiazines from 2'-hydroxy-3',5'-dichloro-4-4'-chlorophenyl chalcone with thiourea, phenyl thiourea and diphenyl thiourea. In this series, we have synthesized 4-(2'-hydroxy-3',5'-dichlorophenyl)-6-(4'-chlorophenyl)-2-imino-1,3-thiazine and 4-(2'-hydroxy-3',5'-dichlorophenyl)-6-(4'-chlorophenyl)-2-iminophenyl-1,3-thiazine from thiourea and phenyl thiourea respectively and 4-(2'-hydroxy-3',5'-dichlorophenyl)-6-(4'-chlorophenyl)-2-iminophenyl-3-phenyl-1,3-thiazine from diphenyl thiourea. The newly synthesized chloro-substituted 1,3-thiazines were screened for their antibacterial activities against *Gram positive* pathogens *Staphylococcus aureus* and *Streptococcus sp.* and *Gram negative* pathogens *Pseudomonas sp.* and *Salmonella typhi*. All these compounds have been characterized on the basis of their UV, IR and NMR spectral studies.

Key Words: Thiazines, Antibacterial activities, Thiourea, Phenyl thiourea, Diphenyl thiourea.

INTRODUCTION

Thiazines is a six membered ring system, which contains two heteroatoms (N and S) placed in the heterocyclic ring at 1,3-positions. Heterocyclic compounds with thiazine ring system have many pharmaceutical activities and play important roles in biochemical processes[1,2]. Many workers have synthesized different 1,3-thiazines[3-6]. Chalcones[7] and their analogues[8] having α,β-unsaturated carbonyl system are regarded as an important framework and served as precursors for physiologically active compounds[9]. The reaction of thiourea with α,β-unsatured ketones results in 1,3-thiazines[10,11]. The presence of 4-phenyl chloro-substituted moiety and 2-substituted imino group present in thiazine ring exhibit antibacterial activities[12]. Encouraged by the earlier reports, we have designed and synthesized some new chloro-substituted 1,3-thiazines from chalcones by using thiourea, phenylthiourea and diphenyl thiourea. These compounds then screened for their antibacterial activities against some Gram positive and Gram negative pathogens.

EXPERIMENTAL

All the chemicals used were of analytical grade. All the solvents used were purified by standard methods. All the glass ware's used in the present work were of pyrex quality. Purity of compounds was monitored on silica gel coated TLC plate. Melting points were determined in glass capillary tubes and are uncorrected. PMR spectra were recorded on a Bruker avance 400 MHz spectrophotometer in $CDCl_3$ and UV spectra on spectrophotometer (Schimadzu UV1601). IR spectra were recorded on a Perkin-Elmer FT IR 1600. Physical characterization data of all the compounds are given in Table-1.

TABLE-1
CHARACTERIZATION DATA OF NEWLY SYNTHESIZED COMPOUNDS

Compound	m.f.	m.p. (ºC)	Yield (%)	R_f
1a	$C_8H_6O_2Cl_2$	53	75	0.83
2a	$C_{15}H_9O_2Cl_3$	190	70	0.86
3a	$C_{16}H_{11}N_2OSCl_3$	100	75	0.63
4a	$C_{22}H_{15}N_2OSCl_3$	175	70	0.83
5a	$C_{27}H_{18}N_2OSCl_3$	145	75	0.70

The synthetic routes which furnished the target compounds are shown below along with their UV, IR and NMR data (**Scheme-I**).

Preparation of 2'-hydroxy-3', 5'-dichloroacetophenone (1a): 2'-Hydroxy-5'-chloroacetophenone (**3g**) was dissolved in acetic acid (5 mL). Sodium acetate (3 g) was added to the reaction mixture and then chlorine in acetic acid reagent (40 mL,

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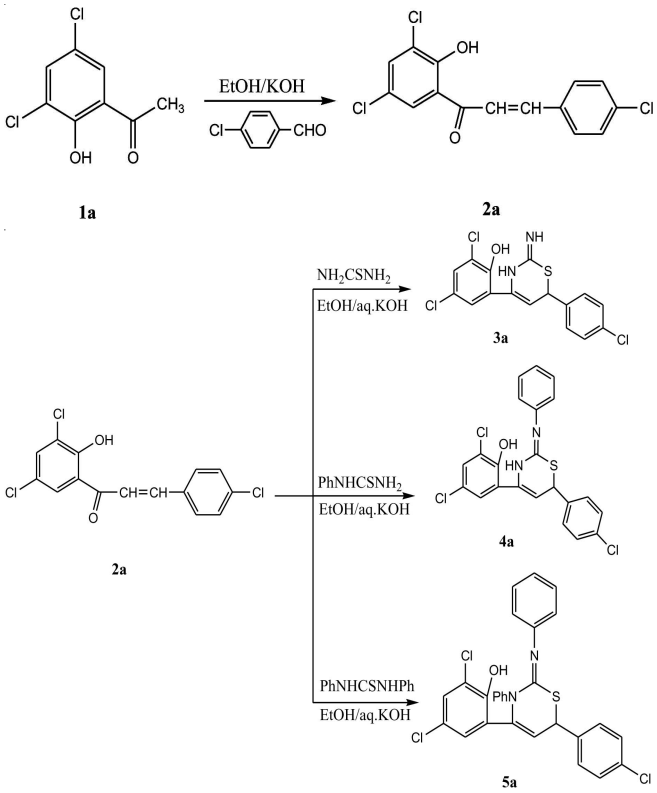
7.5 w/v) was added dropwise with stirring. The temperature of the reaction mixture was maintained below 20 ºC. The mixture was allowed to stand for 0.5 h. It was poured into water with stirring. A pale yellow solid thus obtained was filtered, dried and crystallized from ethanol.



Scheme-I

IR (KBr, ν_{max}, cm^{-1}): 3050 (-OH phenolic), 1645 (C=O in ketone), 1300 (C-O), 730 (C-Cl stretching). PMR: δ 12.73 (s, 1H, Ar-OH); δ 7.25-7.63 (m, 2H, Ar-H); δ 2.60 (s, 3H, $-CH_3$). UV: 343 nm.

Preparation of 2'hydroxy-3',5'-dichloro-4-4'-chlorophenylchalcone (2a): 2'-Hydroxy-3',5'-dichloroacetophenone **(1a)**, (0.1 M) was dissolved in ethanol (50 mL) and *p*-chlorobenzaldehyde (0.1 M) was added and the mixture was heated to boiling. Aqueous potassium hydroxide solution (40 %, 40 mL) was added dropwise with constant stirring. The mixture was stirred mechanically at room temperature for about 0.5 h and kept overnight. It was then acidified by hydrochloric acid solution (50 %). The solid thus separated was filtered, washed with sodium bicarbonate (10 %) followed by water and finally crystallized from ethanol (**2a**).

IR (KBr, ν_{max}, cm^{-1}): 3400 (-OH phenolic), 1647 (C=O in ketone), 1579 (C=C stetching), 818 (C-Cl stretching), 3074 (aromatic -CH stretching). PMR: δ 7.93 (d, 1H, CH = CH); δ 7.52 (d,1H, CH=CH); δ 7.43-7.46 (s, 2H, Ar-H); δ 7.60-7.80 (m, 4H, Ar-H); δ 13.31 (s, 1H, Ar-OH). UV: 380 nm.

Preparation of 4-(2'-hydroxy-3',5'-dichlorophenyl)-6-(4'-chlorophenyl)-2-imino-1,3-thiazine (3a): 2'-Hydroxy-3',5'-dichlorophenyl-4-4'-chlorophenylchalcone (**2a**), (0.01 M) was dissolved in ethanol (25 mL). To this thiourea (0.01 mol) and aqueous KOH solution (0.02 M) were added. The reaction mixture was refluxed for 2.5 h, cooled, diluted with water and acidified with conc. HCl. The product thus obtained was filtered, dried and crystallized from ethanol (**3a**).

IR (KBr, ν_{max}, cm^{-1}): 3393 (-OH phenolic), 2918 (N-H stretching), 3100 (aromatic C-H stretching), 1664 (C=N stretching), 1587 (C=C stretching); 831 (C-Cl) PMR: δ 7.51-7.54 (d, 4H, Ar-H); δ 6.9 to 8 (s, 2H, Ar-H); δ 4.5 (s, 1H, N-H stretching); δ 9.2 (s, 1H, ArOH) UV: 285 nm.

Preparation of 4-(2'-hydroxy-3', 5'-dichlorophenyl)-6-(4'-chlorophenyl)-2-iminophenyl-1,3-thiazines (4a): 2'-Hydroxy-3',5'-dichlorophenyl-4-4'-chlorophenylchalcone (**2a**), (0.01 M) was dissolved in ethanol (25 mL). To this phenylthiourea (0.01 M) and aq. KOH solution (0.02 M) were added. The reaction mixture was refluxed for 2.5 h, cooled, diluted with water and acidified with conc. HCl. The product was filtered, dried and crystallized from ethanol (**4a**).

IR (KBr, ν_{max}, cm^{-1}): 3255 (OH phenolic); 3170 (N-H stretching); 1615 (C=C stretching); 1315 (OH bending in phenol); 843 (C-Cl stretching). PMR: δ 4.6 (s, 1H, NH); δ 7.08-7.31 (m, 9H, Ar-H); δ 6.8 to 8 (s, 2H, Ar-H); 9.74 (s, 1H, ArOH) UV: 330 nm.

Preparation of 4-(2'-hydroxy-3',5'-dichlorophenyl)-6-(4'-chlorophenyl)-2-iminophenyl-3-phenyl-1,3-thiazine (5a): 2'-Hydroxy-3',5'-dichlorophenyl-4-4'-chlorophenylchalcone (**2a**),(0.01 M) was dissolved in ethanol (25 mL). To this diphenylthiourea (0.01 M) and aq. KOH solution (0.02 M) were added. The reaction mixture was refluxed for 2.5 h, cooled, diluted with water and acidified with conc. HCl. The product was filtered, dried and crystallized from ethanol.

IR (KBr, ν_{max}, cm^{-1}): 3045 (OH phenolic); 1600 (C=C stretching); 840 (C-Cl stretching); 1662 (-C=N). PMR: 7 to 7.5 (d, 4H, Ar-H); 6.5 to 7.5 (m, 10H, Ar-H); 9.78 (s, 1H, ArOH) UV: 272 nm.

The compounds (**3a**, **4a** and **5a**) were screened for their antibacterial activity against gram positive pathogens *Staphylococcus aureus* and *Streptococcus sp*. and gram negative pathogens *Pseudomonas sp*. and *Salmonilla 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-2.

TABLE-2
ANTIBACTERIAL ACTIVITIES OF SYNTHESIZED NEW COMPOUNDS

Comp.	Zones of inhibition (nm)			
	Staphylococcus aureus	*Streptococcus sp.*	*Pseudomonas sp.*	*Salmonilla typhi*
3a	12	10	10	12
4a	14	12	14	14
5a	14	15	15	14

RESULTS AND DISCUSSION

All the newly synthesized compounds (**3a**, **4a** and **5a**) were found to be active against test pathogens. However, their activity increases from **3a** to **5a** in accordance with the increase in complexity. A further detailed study in the light of medical sciences is advised to reveal the symbiotic impact of titled compounds in curing human ailments.

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