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Synthesis and microbial studies of novel 1, 3-thiazine compounds bearing schiff base moiety

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ABSTRACT

The present investigations describe about the synthesis, characterization and biological studies of novel 1,3-thiazine derivatives. These compounds are synthesized by performing reaction between thiourea and various chalcones derived by claisen-schimidt reaction between various schiff bases of p-NH_2-acetophenone and p-Cl-benzaldehyde. The structures of all the synthesized compounds were elucidated by using spectral data and anti-microbial activity studied by using disc diffusion method.

Key words: p-NH_2-acetophenone, chalcones, schiff bases, 1,3-thiazines, antibacterial activity.

INTRODUCTION

Thiazines are heterocyclic compounds having four carbon atoms, one nitrogen, one sulphur atom at various positions in the six member ring and exist as 1,2; 1,3 and 1,4 isomers [1-3]. However their derivatives having N-C-S linkage have been used in the fields of medicinal and pharmaceutical chemistry and reported to exhibit a variety of biological activities. Like, antitubercular, antibacterial, antimicrobial, antitumor, insecticidal, fungicidal and herbicidal agents [4-13]. The 1, 3-thiazines are great importance because they form part of the framework of cephalosporins (3,6-dihydro-2H,1,3-thiazine) and also in some other medicinally important compounds like Xylazin (agonist at the α-2 class of adrenergic receptor is used for sedation, anesthesia, muscle relaxation, and analgesia in animals), Chlormezanone (used as an anxiolytic and a muscle relaxant) etc. Further, 1,3-thiazine core moieties have remarkable potential of anti radiation agents and also used in organic synthesis and transformations as reaction intermediates [14-15].

MATERIALS AND METHODS

General: Chemicals were procured from E. Merck (India), S. D. Fine Chemicals (India) and reagent/solvents were used without distillation procedure. Melting points were taken in open capillary tubes and are uncorrected. IR (KBr) spectra were recorded on a Perkin-Elmer 157 infrared spectrometer (ν in cm^{-1}) and NMR spectra were recorded on a Bruker spectrometer DPX-300MHz (Bruker, Germany) by using $CDCl_3$ as solvent with TMS as an internal standard. All the spectral data are consistent with the assigned structures of the desired product and the progress of the reactions was monitored on silica gel G plates using iodine vapour as visualizing agent.

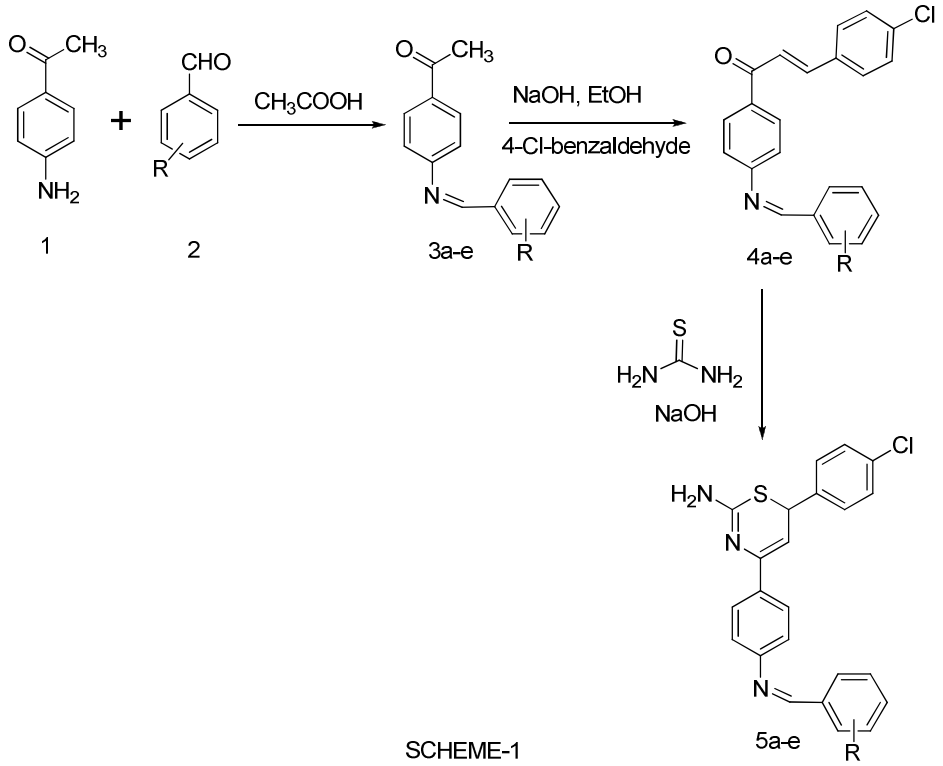
1. General procedure for preparation of schiff bases (3a-e) :
A mixture of 4-NH_2-acetophenone (0.01mole) and substituted benzaldehyde (0.01mole) were taken in pestle and morter with catalytic amount of acetic acid. The mixture was grinded continuously for 10-15 min at room temperature. The progress of the reaction was monitored by using TLC-technique. After completion of the reaction indicated by TLC, the mixture was poured in crushed ice and acidified with dilute NH_4OH if needed. The solid separated was filtered and recrystalyzed from ethanol.

2. General procedure for preparation of chalcones (4a-e):
A mixture of schiff base (0.01mole) and p-chlorobenzaldehyde (0.01mole) were stirred in ethanol for 2-3 hour with aqueous NaOH in distilled ethanol (20 mL). The progress of the reaction was monitored by using TLC-technique. After completion of the reaction, the mixture was poured in ice cold water, solid formed was filtered off, dried and recrystalyzed from ethanol.

3. General procedure for preparation of 1, 3-thiazine derivatives (5a-e):
The mixture of chalcone (0.01mole) and thiourea (0.01mole) was refluxed in ethanol with catalytic amount of NaOH by using round bottom flask. The reaction was monitored by TLC and after completion of reaction, the content were cooled to room temprature and poured into beaker containing crushed ice, the solid obtained was filtered, washed with water and finally recrystalyzed from ethanol.

RESULTS AND DISCUSSION

The schiff bases **3a-e** were synthesized by using condensation reaction between p-NH_2-acetophenone and substituted benzaldehyde in the presence of catalytic amount of acetic acid at room temperature by grinding technique. The schiff base obtained from the above step was allowed to react with p-Cl-benzaldehyde in ethanol with aqueous NaOH produced chalcones **4a-e**. The target product 1, 3-thiazine derivatives **5a-e** were obtained by the cyclyzation reaction between chalcones and thiourea with catalytic amount of NaOH in ethanol medium under reflux condition for 3-4 hours **(Scheme-1).**



SCHEME-1

In UV-Vis spectra, formation of schiff base was confirmed by appearance of additional band at 352.37nm which may be due C=N chromophore. The formation of chalcone was confirmed by the increased λ_{max} values from 308.08 to 326.13 nm of π- π* and 352.37 to 365.00 of n- π* transition of carbonyl group respectively. The disappearance of weak doublet peak of NH_2 in the IR spectra of **3a** around 3325.03 indicated that the formation of schiff base. Hence the stretching frequency of C=O group decreased from 1613.8 to 1583.8 in the **4a** indicated that the formation of chalcone because conjugation decreased the C=O bond order. The appearance of two new NH bands around 3373.09-3207.36 cm^{-1} in the **5a** indicated the formation of 1,3-thiazine derivatives. The formation of schiff base was confirmed by appearance CH=N proton around 8.4ppm and formation of chalcone was confirmed by the appearance of two doublets around 7.48-7.53ppm is due to CH=CH-CO group. The compounds **5a-e** showed the following characteristic signals both in ^{1}H-NMR and ^{13}C-NMR spectra and these have supported for our proposed structure. The two doublets around 4.5-5.5ppm (some cases multiplets was appeared) are belongs to two protons attached with 5^{th} and 6^{th} carbons. The NH_2 protons showed a broad singlet at 8.01ppm, CH=N and 12-Ar-H appeared around their respective regions. The ^{13}C-NMR-spectra of **7b** showed the following carbon signals 49.75 (OCH_3), 54.64 (C-6), 111.44 (C-5), 158.01(CH=N), 151.35 (C-NH_2), 145.77 (C-Cl), 113.4, 113.8, 114.3, 117.7, 120.3, 127.9, 128.2, 129.2, 129.5, 129.8, 130.2,131.0, 131.7, 131.8,133.8,139.0,149.5,150.0 (18Ar-C). The antimicrobial activity of all the 1,3-thiazine compounds showed good inhibition zone against selective bacterial growth where as there is no considerable effect against fungal growth (table-2).

Table-1: Physical data of synthesized compounds 5a-e

Code	R	Yield (%)	Mp (^{o}C)	R_f value
5a	p-Me	90	173-175	0.75
5b	p-OMe	85	132-134	0.75
5c	p-Cl	85	160-162	0.65
5d	p-NO_2	80	158-160	0.60
5e	m-NO_2	78	140-142	0.57

Table-2: Antimicrobial data of synthesized compounds 5a-e

S. No.	Sample	**Zone of Inhibition** (mm in diameter, 20 µg/disc)		
		Escherichia coli	***Staphylococcus aureus***	***Aspergillus niger***
1	**PC***	**13**	**18**	**14**
2	**5a**	**10**	**09**	**-**
3	**5b**	**16**	**12**	**-**
4	**5c**	**13**	**11**	**06**
5	**5d**	**10**	**15**	**08**
6	**5e**	**08**	**12**	**-**

**Gentamicin (10 µg) for Bacteria, * Ketoconazole (10 µg) for Fungi*

CONCULUSION

We have synthesized a series of new 1, 3-thiazine derivatives obtained with good yield. All the compounds were characterized by using UV-Vis, IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. We observed that all the 1,3-thiazine compounds showed good antibacterial activity than the antifungal activity.

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