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Synthesis and antimicrobial activity of some 2 – aryl - 3 - [(4 - methyl cinnamoyl amino) - 4 - oxo – thiazolidines with synthesis and antimicrobial activity of some 2 – (4-hydroxyphenyl) - 3 - [(4 - methyl cinnamoyl amino) - 4 - oxo – thiazolidines

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ABSTRACT

Compounds 2–(4-hydroxyphenyl) – 3 – [(4 – methyl cinnamoyl) amino] 4 - oxo - thiazolidine (IVa-h) have been synthesized by cyclisation of acyclic compounds and thioglycolic acid on Schiff 's bases. All the products have been evaluated for their in vitro antimicrobial activity against various strains of bacteria.

Key words: Thiazolidines and antimicrobial activity.

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INTRODUCTION

The chemistry of heterocycles lies at the heart of drug discovery [1]. Nitrogen and Sulfur containing heterocyclic compounds like 4-oxo-thiazolidines are known to possess wide range of activities such as anticonvulsant [2], anti–inflammatory [3], anti-tubercular activity [4], anthelmintic activity [5], antiviral activity [6], antifungal activity [7], antibacterial activity [8], anticancer [9] and anti - HIV activity [10] etc. Moreover 4-oxo-thiazolidines are non toxic.

4-oxo-thiazolidine with styryl moiety has shown antibacterial, anti - HIV and anticancer activities. These interesting biological activities have attracted our attention to the chemistry of nitrogen and sulfur containing heterocycles. Hence it was thought of interest that 4-oxo-thiazolidine, if coupled to styryl moiety; the resulting compounds may possess significant biological potency.

4 - Oxo - thiazolidines are synthesized either by cyclisation of acyclic compounds or by interconversion among appropriately substituted thiazolidinone derivatives by the action of thioglycolic acid on Schiff's bases [11]. The reaction undergoes by the attack of the mercapto acetic acid upon the C = N group, with the - S - CH_2 - COOH adding to the carbon atom followed by the capture of a proton by nitrogen and subsequent cyclisation. The nucleophilic attack of mercaptoacetic acid anion on carbon of azomethine, which has got positive character while nitrogen has negative character, is evidenced [12]. Simultaneous removal of water as it forms in reaction helps in condensation and determination of the reaction time. The constitution of all the products has been characterized using elemental analyses, IR, 1^H NMR and mass spectral study. All the compounds were screened for their *in vitro* antimicrobial activity against different strains of bacteria.

EXPERIMENTAL

All the melting points are determined in open capillary tubes and are uncorrected. Thin layer chromatography was used for monitoring the reaction and to check purity. IR spectra recorded on Bio – Rad FTS – 40 spectrophotometer on KBr disc. 1^H NMR spectra were recorded on a model DPX – 200 Brucker FT – NMR instrument using TMS as an internal standard. FAB mass spectra were recorded on JEOL SX 102/DA 6000 spectrophotometer. All the compounds gave satisfactory elemental analyses.

PREPARATION OF 2 – (4-HYDROXYPHENYL) - 3 - [(4 - METHYL CINNAMOYL AMINO) - 4 - OXO – THIAZOLIDINES

Preparation of 1 – (4-hydroxy benzylidine)– 2 – [(4 – methyl cinnamoyl)] hydrazine (III)

4 – Methyl cinnamoyl hydrazine (1.76 g; 0.01 M) was dissolved in methanol (30 ml) and 4-hydroxy benzaldehyde (1.22 g; 0.01 M) in methanol (10 ml) was slowly added. The reaction mixture was refluxed for 3 hours on water bath. The resulting mass was allowed to cool at room

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temperature; product separated was filtered and washed with ice cold methanol, dried and recrystallised from ethanol (95 %). Yield : 1.3 g;(73.86 %) ; M.P. : 170^{O}C

Preparation of 2–(4-hydroxyphenyl) – 3 – [(4 – methyl cinnamoyl) amino] 4 - oxo - thiazolidine (IV)

To a solution of 1 – benzylidine – 2 – [(4 – methyl cinnamoyl)] hydrazine (2.64 g; 0.01 M) in 1: 4 dioxane (25 ml) was added thioglycolic acid (0.925 g; 0.01 M). The mixture was refluxed at 110 - 115^{O}C for 8 hours. The reaction mixture was allowed to cool at room temperature and triturated with 10 % sodium bicarbonate solution to remove unreacted mercaptoacetic acid. The solid product thus separated was filtered and washed with water. Recrystallised from ethanol (95 %). Yield: 2.8 g; (78.87%); M.P.: 236^{O} C. M.F. : $C_{19}H_{18}N_2O_3S$; M.W.: 354.42 ; Required : N , 7.90 %, S,9.05% Found : N , 7.65 %. S , 8.80 %. TLC solvent system: Acetone: Benzene (4:6). IR (KBr) in υ max cm^{-1} : 3275 (-OH of phenyl ring) 1639 & 1655 (acyclic and cyclic carbonyl respectively). 690 (C-S-C- linkage of thiazolidine ring), 814 (para substituted Phenyl ring), 1150 (-C-O str.); 3209 (N-H str.); 953 (di substituted alkene) . 1^{H} NMR in δ ppm ; 10.28 (s, 1H, Phenolic –OH) , 9.53 (s, 1H, - NH) , 6.8 – 7.8 (m, 8H, Aromatic protons) , 3.5 (s, 2H , - CH_2 , Thiazolidine ring) , 3.33 (s, 1H , N – CH – Ar) , 2.3 (dd, 2H , - CH = CH -), 1.68 (s, 3H , Ar - CH_3) δ ppm. Similarly, other 4 - oxo - thiazolidines were prepared. The physical data are recorded in Table 1.

Table 1 : Physical Constants of the compounds 1a-h

Comp. No.	Aryl	MOLECULAR FORMULA	M.W.	M.P. ^{o}C	% OF YIELD	% OF NITROGEN	
						REQ.	FOUND
IVa	C_6H_5-	$C_{19}H_{18}N_2O_2S$	338.42	60	76	8.27	8.22
IVb	4-OH-C_6H_4-	$C_{19}H_{18}N_2O_3S$	354.42	236	77	7.90	7.89
IVc	2-OH-C_6H_4-	$C_{19}H_{18}N_2O_3S$	354.42	194	81	7.90	7.89
IVd	3-OH-C_6H_4-	$C_{19}H_{18}N_2O_3S$	354.42	176	80	7.90	7.88
IVe	2,4-$(OH)_2C_6H_3$-	$C_{19}H_{18}N_2O_4S$	370.42	160	74	7.56	7.50
IVf	4-OCH_3-C_6H_4-	$C_{20}H_{20}N_2O_3S$	368.45	135	76	7.60	7.56
IVg	2-OCH_3-C_6H_4-	$C_{20}H_{20}N_2O_3S$	368.45	75	76	7.60	7.57
IVh	3,4-$(OCH_3)_2$-C_6H_3-	$C_{21}H_{22}N_2O_4S$	398.47	119	75	7.03	7.00

RESULTS AND DISCUSSION

Compounds **1a - h** were screened for their in vitro antibacterial activity using cup-plate agar diffusion method [13] at a concentration of 40 µg/ml using gram positive bacterial strains such as Staphylococcus and gram negative bacterial strain such as *Escherichia coli*. Known antibiotics like ampicillin, amoxycillin, norfloxacin, penicillin and greseofulvin were used for comparison purpose. By visulizing the antimicrobial data, these compounds have no noteworthy activity as observed in Table No.2. Interestingly some of these have smaller zone of inhibition as compared to solvent. Compounds no. 1e, 1g, and have good activity against *S.aureus* and compoundsno.1b, 1c and 1g have also possess good activity against *E. coli*. Antimicrobial results of all compounds are given in Table-2.

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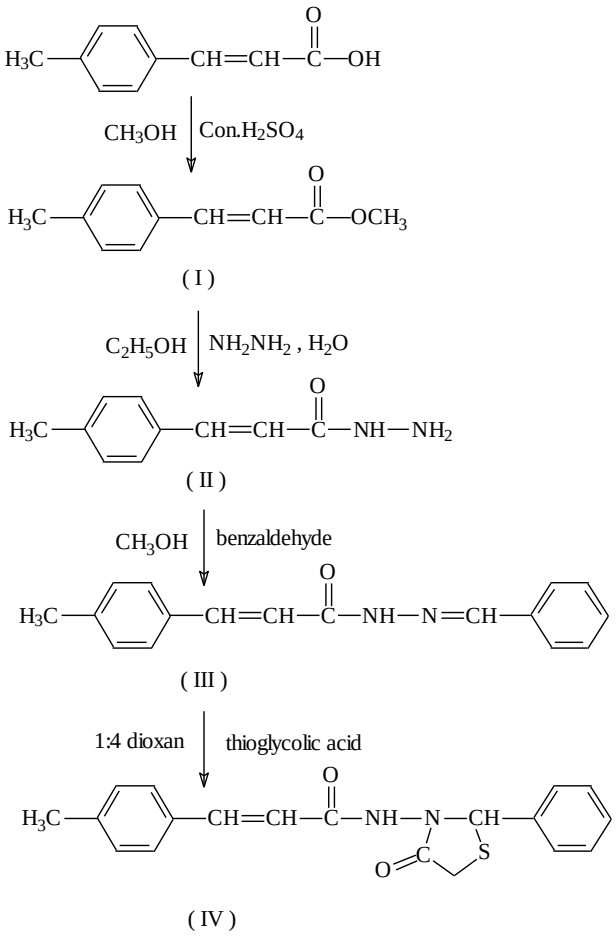
Table-2 : Antimicrobial activity of the compounds 1a-h

Comp. No.	Aryl	Zone of inhibition in mm.	
		E.coli	*S.aureus*
IVa	C_6H_5-	11	10
IVb	4-OH-C_6H_4-	13	10
IVc	2-OH-C_6H_4-	13	11
IVd	3-OH-C_6H_4-	12	11
IVe	2,4-$(OH)_2C_6H_3$-	11	14
IVf	4-OCH_3-C_6H_4-	11	12
IVg	2-OCH_3-C_6H_4-	14	13
IVh	3,4-$(OCH_3)_2$-C_6H_3-	11	10

SCHEME



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