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Biological studies of some novel 2 – aryl - 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 (IVi-o) have been synthesized by the reaction of thioglycolic acid on Schiff 's bases. All the products have been evaluated for their in vitro antimicrobial activity against two strains of bacteria S. aureus and E. coli .

Key words: Thiazolidines and antimicrobial activity.

INTRODUCTION

In continuation of the search of potent molecules, the title compounds were synthesized. The thiazolidines exhibit broad spectrum of biological activities, possibly due to the presence of toxophoric N-C-S moiety(1).Compounds containing thiazole moieties have been reported to possess biological activity, especially antifungal(2), antimicrobial(3,4), and antiprotozoal properties(5,6). Heterocyclic compounds like 4-oxo-thiazolidines are known for their wide range of activities such as, anti-tubercular activity(7), anthelmintic activity (8), Antiviral activity(9), Anticancer(10) and Anti - HIV activity(11) etc. Moreover 4-oxo-thiazolidines are non toxic.

4 - Oxo - thiazolidines are synthesized either by cyclisation of acyclic compounds or by inter conversion among appropriately substituted thiazolidinone derivatives by the action of thioglycolic acid on Schiff ' s bases(12). 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 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.

MATERIALS AND METHODS

All the melting points are determined in open capillary tubes and are uncorrected. 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 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^OC

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^OC for 8 hours. The reaction mixture was allowed to cool at room temperature and triturated with 10 % sodium bicarbonate solution to remove un reacted 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 Pheyl 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**.

SCHEME

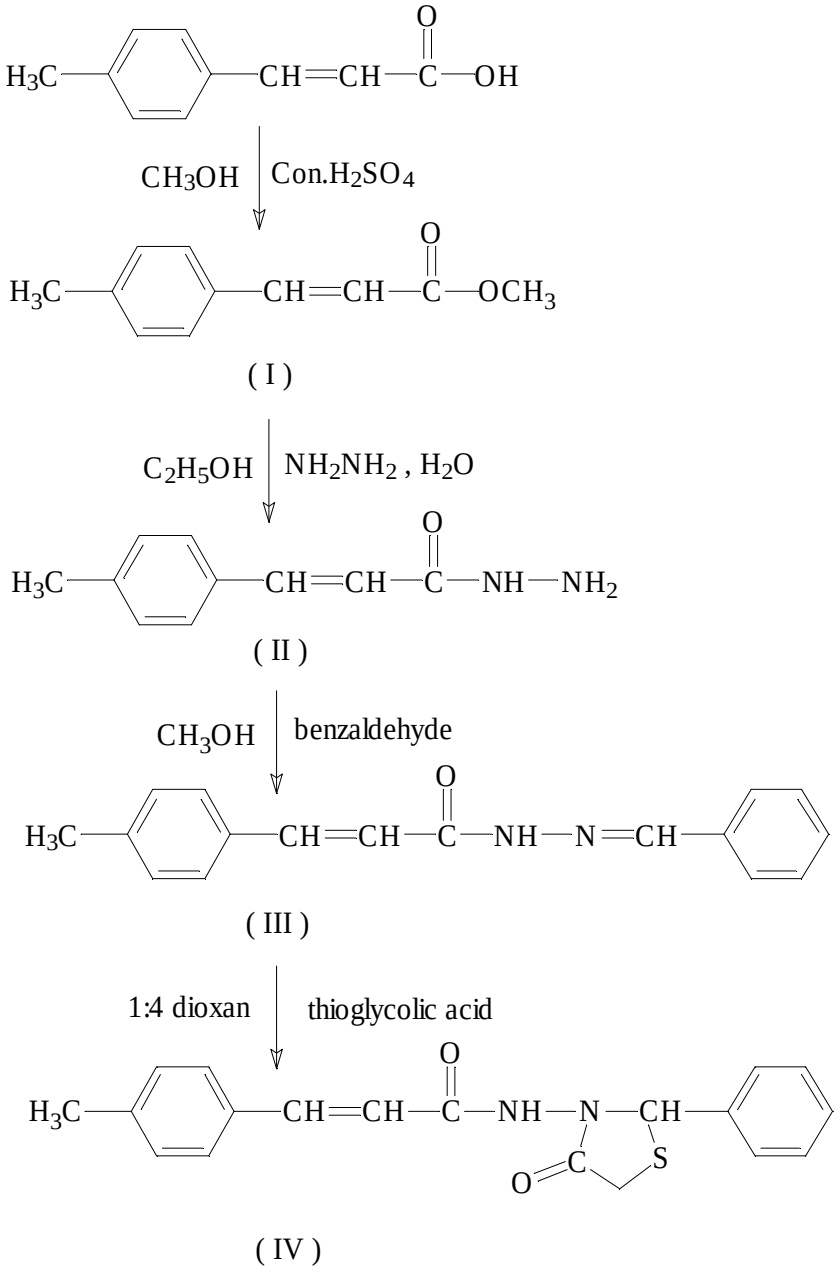
H3C
CH=CH—C—OH
O
CH3OH
Con.H2SO4
H3C
CH=CH—C—OCH3
O
(I)
C2H5OH
NH2NH2 , H2O
H3C
CH=CH—C—NH—NH2
O
(II)
CH3OH
benzaldehyde
H3C
CH=CH—C—NH—N=CH
O
(III)
1:4 dioxan
thioglycolic acid
H3C
CH=CH—C—NH—N—CH
O
C
S
O
(IV)

Table 1 : Physical Constants of the compounds 1i-o

Comp. No.	Aryl	Molecular formula	M.w.	M.p. ^{O}c	% of yield	% of nitrogen	
						Req.	Found
1i	3,4,5$(OCH_3)_3C_6H_2$-	$C_{22}H_{24}N_2O_5S$	428.50	151	80	6.53	6.50
1j	4(OH),3$(OCH_3)C_6H_3$-	$C_{20}H_{20}N_2O_4S$	384.44	126	65	7.28	7.24
1k	4$(CH_3)C_6H_4$-	$C_{20}H_{20}N_2O_2S$	352.45	82	64	7.94	7.91
1l	4(Cl)C_6H_4-	$C_{19}H_{17}N_2O_2SCl$	372.86	86	72	7.51	7.46
1m	4$(NO_2)C_6H_4$-	$C_{19}H_{17}N_3O_4S$	383.42	120	78	10.95	10.90
1n	3,4,-O-(CH_2)-O-C_6H_3-	$C_{20}H_{18}N_2O_4S$	382.42	243	71	7.32	7.30
1o	C_6H_5-CH=CH-	$C_{21}H_{20}N_2O_2S$	364.46	108	77	7.68	7.61

RESULTS AND DISCUSSION

Compounds **1i - o** 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. 1i, 1j, 1k, 1m and 1o have good activity against *E. coli* and compoundsno.1j, 1k and 1i have also possess good activity against *S.aureus.* Other compounds are moderate active. Antimicrobial results of all compounds are given in **Table-2**.

Table-2 : Antimicrobial activity of the compounds 1i-o

Comp. No.	Aryl	Zone of inhibition in mm.	
		E.coli	*S.aureus*
1i	3,4,5$(OCH_3)_3C_6H_2$-	12	12
1j	4(OH),3$(OCH_3)C_6H_3$-	12	14
1k	4$(CH_3)C_6H_4$-	13	13
1l	4(Cl)C_6H_4-	11	11
1m	4$(NO_2)C_6H_4$-	14	11
1n	3,4,-O-(CH_2)-O-C_6H_3-	11	10
1o	C_6H_5-CH=CH-	14	10

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