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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL 2-(4-SUBSTITUTED PHENYL)-3-(4-SUBSTITUTED PHENYL)-5-METHYLTHIAZOLIDIN-4-ONES.

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ABSTRACT

The main objective of the medicinal chemistry is to synthesize the compounds that show promising activity as therapeutic agents with lower toxicity. 4-thiazolidinone derivatives are very useful compound with well known biological activity. Notable among these are antibacterial, antiviral ,antifungal, analgesic, anti-inflammatory, antitubercular and anticonvulsant. In the current research work, the title compounds 2-(4-substituted phenyl)-3-(4-substituted phenyl)-5-methylthiazolidin-4-ones were synthesized by condensing 4-substituted anilines with 4-substituted benzaldehydes by using ethanol as solvent. The synthesized compounds were heated with 2-mercaptopropionic acid in excess of benzene. The identification and characterization of the synthesized compounds were carried out by Elemental analysis, melting point,Thin Layer Chromatography, FT-IR, NMR and Mass data to ascertain that all synthesized compounds were of different chemical nature than the respective parent compound. The compounds were screened for antibacterial and antifungal activity.

The antibacterial activity conducted against *Staphylococcus aureus* (ATCC 6538) as a Gram +ve microorganism and *Escherichia coli* (ATCC 8739) *as a* Gram -ve microorganism using Ampicillin and Penicillin-G as a reference standard.

The compounds II_a ,II_d and II_f found to possess better antibacterial activity than Ampicillin and Penicillin (Reference standard) in MIC(Minimum inhibitory concentration).

KEYWORDS: Ampicillin, MIC, Penicillin, 4-thiazolidinone,

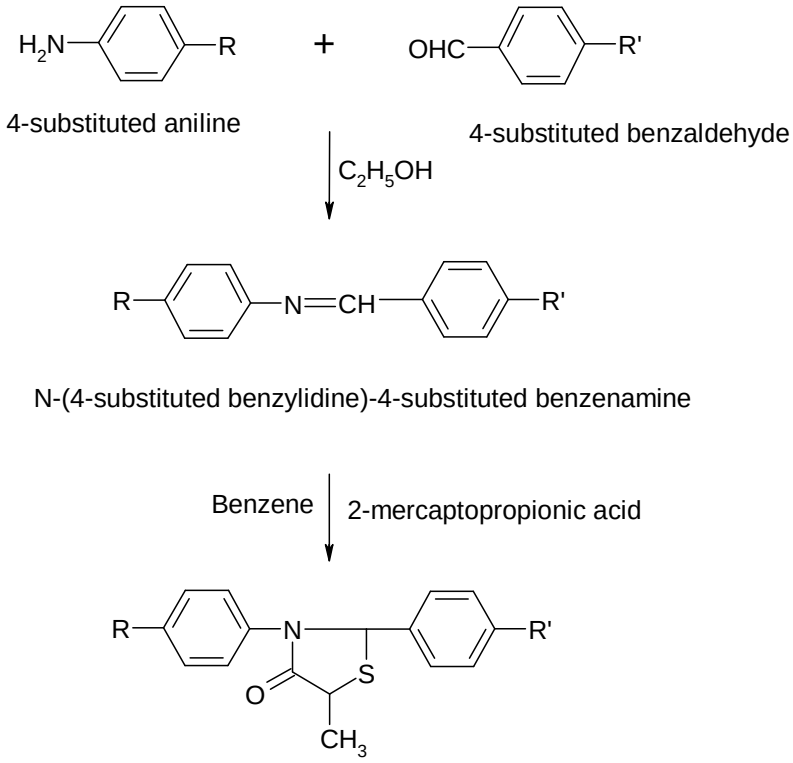
INTRODUCTION

4-Thiazolidinones have been reported to show a broad spectrum of biological activities. Notable among these are antibacterial[1], anti-inflammatory[2], antitubercular[3], anticonvulsant[4], local anesthetic[5] and Anthelmintic activity[6,7]. The pharmacological properties of 4-thiazolidinones encouraged our interest in synthesizing several new compounds featuring various heterocyclic rings, attached to 4-thiazolidinone moieties. As a part of our aim to search for biologically active heterocycles containing sulfur and nitrogen, we have now synthesised a series of some novel 2-(4-substituted phenyl)-3-(4-substituted phenyl)-5-methylthiazolidin-4-ones. The fluoro, bromo, methoxy, hydroxy, nitro substitutions at para position improve antimicrobial activity. Therefore it was though worthwhile to synthesize some new thiazolidinone containing compounds and evaluate antimicrobial potential.

MATERIALS AND METHODS

All the reagents and solvents used were of laboratory grade. The melting points of synthesized compounds were determined by open capillary method and were uncorrected. The purity and homogeneity of compounds were checked using TLC technique. IR spectra[8] of compounds were recorded using KBr pellets on Perkin Elmer 337 spectrophotometer. ^{1}H-NMR spectra[9] were recorded on Bruker Avance-300 MHz Spectrophotometer using dimethyl sulfoxamide as solvent at Indian Institute of Technology(IIT), Mumbai. Mass Spectra of the synthesized compounds were recorded on Liquid Chromatography Mass Spectrometer at Indian Institute of Technology(IIT), Mumbai. The compounds were also subjected to C, H, N and S analysis(ThermoFinnigan) at IIT Mumbai.

Scheme of synthesis



2-(4-substituted phenyl)-3-(4-substituted phenyl)-5-methylthiazolidin-4-one

A. **Preparation of N-(4-Substituted benzylidine)-4-Substituted benzenamine:**

In a 500ml round bottom flask equipped with reflux condenser, 4-substituted anilines (5gm, 1mol) and 4-substituted benzaldehydes (5gm, 1mol) were dissolved in ethyl alcohol in excess solvent. Reflux for 4h. The reaction mixture were allowed to cool at room temperature. Solid separated by evaporation solvent. The products were recrystallised by using Ethanol:Ethyl acetate(1:1).

B. Preparation of 2-(4-substituted phenyl)-3-(4-substituted phenyl)-5-methylthiazolidin-4-one:

Compound 1(0.1mol) were heated with 2-mercaptopropionic acid (0.2mol) in excess of benzene solvent. Reflux for 5h. The reaction mixture cooled at room temperature. Solid separated by evaporation of solvent. The products were recrystallised by Ethanol:Dioxane(1:1).

C. Antimicrobial Screening[10]:

All the synthesized compounds were subjected to *in vitro* antimicrobial screening by the tube dilution technique against various species of gram-positive and gram-negative bacteria *Staphylococcus aureus* (ATCC 6538) and *Escherichia coli* (ATCC 8739) using Muller-Hinton broth as the culture medium. Muller Hinton broth (sterilised) was dispensed in each borosilicate test tube (150 x 20 mm). The stock solution was sterilized by passing through a 0.2 mm polycarbonate sterile membrane (Nuclepore) filters. Further the serial dilution of test compounds were carried out by using suitable solvent dimethylformamide and test compounds at various concentrations were added to culture medium in a sterilized borosilicate test tube and different bacterial strains were inoculated at 10^6 bacilli/mL concentration. The tubes were incubated at 37° for 24 h for antibacterial activity and then examined for the presence or absence of growth of the test organisms. All experiments were performed in triplicate. The lowest concentration which showed no visible growth was taken as an end point (MIC).

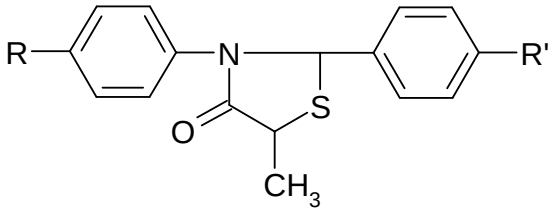
The MIC values were also tested for standard antibiotics (Ampicillin and Penicillin-G) to compare the antibacterial activity of test compounds.

• Physical data of compound. No. II_a-II_f were summarized in Table No.1:

Compd No.	**R**	**R'**	**Molecular formula**	**mp (^{0}C)**	**Yield**	**R_f value**
II_a	F	OH	$C_{16}H_{14}O_2NSF$	130-132	69	0.56
II_b	Br	NO_2	$C_{15}H_{13}O_3N_2SBr$	158-160	70	0.51
II_c	Br	OH	$C_{16}H_{14}O_2NSBr$	120-122	57.53	0.76
II_d	F	$N(CH_3)_2$	$C_{18}H_{18}ON_2SF$	123-125	67	0.65
II_e	Br	OCH_3	$C_{16}H_{16}O_2NSBr$	150-152	61.32	0.54
II_f	NO_2	Cl	$C_{16}H_{13}O_3N_2SCl$	126-128	46.35	0.71

• Elemental analysis of compound. No. II_a-II_l were summarized in Table No.2:

Compd No.	R	R'	Molecular formula	Elemental Analysis (%)							
				Calculated				Found			
				C	H	N	S	C	H	N	S
II_a	F	OH	$C_{16}H_{14}O_2NSF$	64.3	5.1	4.53	0.81	64.2	5.06	4.49	0.77
II_b	Br	NO_2	$C_{15}H_{13}O_3N_2SBr$	55.7	3.6	4.77	0.82	55.7	3.60	4.73	0.78
II_c	Br	OH	$C_{16}H_{14}O_2NSBr$	71.5	6.3	10.0	0.82	71.4	6.35	10.0	0.78
II_d	F	$N(CH_3)_2$	$C_{18}H_{18}ON_2SF$	47.8	2.8	7.88	0.81	47.8	2.85	7.84	0.77
II_e	Br	OCH_3	$C_{16}H_{16}O_2NSBr$	56.7	4.3	3.53	0.001	56.6	4.32	3.49	0.00
II_f	NO_2	Cl	$C_{16}H_{13}O_3N_2SCl$	52.9	4.4	15.8	0.82	52.9	4.38	15.7	0.78



2-(4-substituted phenyl)-3-(4-substituted phenyl)-5-methylthiazolidin-4-one

- **Compound 1: 3-(4-fluorophenyl)-2-(4-hydroxyphenyl)-5-methylthiazolidin-4-one**

  Percentage Yield- 69%, **M.P.**130-132°, **R_f**-0.56 (Ethanol:Dioxane).

  IR (KBr) cm^{-1}: 3404.18 cm^{-1} (-OH), 1703.06 cm^{-1} (C=O), 3045.42 cm^{-1} (Ar–H), 1308.89 cm^{-1} (C-N), **^{1}H NMR:** ($CDCl_3$) δ 6.7-7.0 (m, 8H, Ar-H), δ 1.4 (δ, 3H, CH-CH_3), δ 5.45 (s, 1H, S-CH-N), and δ 8.3 (s, 1H, Ar-OH).

  LC-MS: (m/z, 100%): 302 ([M^+], 100%).

- **Compound 2:** 3-(4-bromophenyl)-5-methyl-2-(4-nitrophenyl)thiazolidin-4-one

  Percentage Yield-70%, **M.P.** 158-160^0, **R_f**-0.51(Ethanol:Dioxane).

IR (KBr) cm^{-1}: 1509.97 cm^{-1} (-NO_2), 1703.06 cm^{-1} (C=O), 3079.92 cm^{-1} (Ar–H), 1341.79 cm^{-1} (C-N), **^{1}H NMR:** ($CDCl_3$) δ 7.0-7.9 (m, 8H, Ar-H), δ 1.6 (δ, 3H, CH-CH_3), δ 5.7 (s, 1H, S-CH-N), **LC-MS:** (m/z, 100%): 392 ([M^+], 100%).

- **Compound 3:** 3-(4-bromophenyl)-2-(4-hydroxyphenyl)-5-methylthiazolidin-4-one

  Percentage Yield- 57.53%, **M.P.** 120-122^0**, R_f**-0.76 (Ethanol:Dioxane).

  IR (KBr) cm^{-1}: 3404.18 cm^{-1} (-OH), 1703.06 cm^{-1} (C=O), 3085.36 cm^{-1} (Ar–H); 1325.94 cm^{-1} (C-N), **^{1}H NMR:** ($CDCl_3$) δ 7.1-7.9 (m, 8H, Ar-H), δ 1.45 (δ, 3H, CH-CH_3) δ 5.7 (s, 1H, S-CH-N), and δ 9.9 (s, 1H, Ar-OH),

  LC-MS: (m/z, 100%): 363 ([M^+], 100%).

- **Compound 4:** 2-(4-(dimethylamino)phenyl)-3-(4-fluorophenyl)-5-methylthiazolidin-one.

  Percentage Yield- 67%, **M.P.** 123-125^0**, R_f**-0.65(Ethanol:Dioxane).

  IR (KBr) cm^{-1}: 1657.79 cm^{-1} (C=O), 3062.54 cm^{-1} (Ar–H); 1333.34 cm^{-1} (C-N).

  ^{1}H NMR: ($CDCl_3$) δ 6.8-7.6 (m, 8H, Ar-H), δ 1.4 (δ, 3H, CH-CH_3), δ 5.8 (s, 1H, S-CH-N), and δ 3.6-4.0 (m, 6H, N(CH_3)$_2$). **LC-MS:** (m/z, 100%): 329([M^+], 100%).

- **Compound 5:** 3-(4-bromophenyl)-2-(4-methoxyphenyl)-5-methylthiazolidin-4-one

  Percentage Yield- 61.32%, **M.P.**150-152 ^{0}**, R_f**-0.54 (Ethanol:Dioxane).

  IR (KBr) cm^{-1}: 1698.65 cm^{-1} (C=O), 1315.66 cm^{-1} (C-N), 3007.64 cm^{-1} (Ar–H); 1258.90 cm^{-1} (ether group in ring). **^{1}H NMR:** ($CDCl_3$) δ 7.3-7.9 (m, 8H, Ar-H), δ 1.7 (δ, 3H, CH-CH_3), δ 5.8 (s, 1H, S-CH-N), and δ 3.8 (s, 3H, Ar-OCH_3).

  LC-MS: (m/z, 100%): 377 ([M^+], 100%).

- **Compound 6:** 2-(4-chlorophenyl)-5-methyl-3-(4-nitrophenyl)thiazolidin-4-one

Percentage Yield- 46.35%, **M.P.** 126-128^0**,** $\mathbf{R_f}$-0.71 (Ethanol:Dioxane).

IR (KBr) cm^{-1}: 1532.64 cm^{-1} (-NO_2), 1698.55cm^{-1} (C=O), 3078.10 cm^{-1} (Ar–H); 1321.32 cm^{-1} (C-N). **^{1}H NMR:** ($CDCl_3$) δ 6.5-7.3 (m, 8H, Ar-H), δ 1.6 (δ, 3H, CH-CH_3), δ 5.7 (s, 1H, S-CH-N). **LC-MS:** (m/z, 100%): 347 ([M^+], 100%).

RESULTS AND DISCUSSION

Antimicrobial activity of 4-thiazolidinone derivatives summarized in Table No.3:

Comp. no	R	R'	Antibacterial Activity	
			Gram Positive Organism	Gram Negative Organism
			S.aureus (µg/ml)	E.coli (µg/ml)
II_a	F	OH	16	16
II_b	Br	NO_2	08	04
II_c	Br	OH	08	02
II_d	F	$N(CH_3)_2$	32	64
II_e	Br	OCH_3	08	02
II_f	NO_2	Cl	16	16
Std 1	Ampicilin		12.5	25
Std 2	Penicillin-G		0.01	0.015

The results revealed that the test compounds II_a, II_d and II_f exhibits remarkable antibacterial activity against *Staphylococcus aureus* (ATCC 6538) as a Gram +ve microorganism and *Escherichia coli(ATCC 8739) as a* Gram -ve microorganism using Ampicillin and Penicillin-G as a reference standard.

The MIC (Minimum inhibitory concentration) values were found in the range of 2 to 64 mg/ml.

CONCLUSION

The some 4-thiazolidinone substituted compounds exhibits remarkable antibacterial activity. Hence, the work presented in this paper is yet another humble effort in the field of medicinal chemistry and sincerely contribute to a healthier and happier human life.

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