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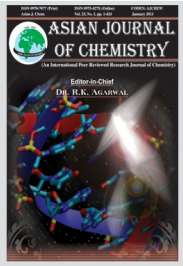

NOTE

Synthesis and Antitubercular Activity of Some 2-(4-Substituted phenyl)-3-(4-substituted phenyl)-5-methylthiazolidin-4-ones

SUNILA T. PATIL[1,*] and PARLOOP A. BHATT[2]

[1]Department of Chemistry, Jodhpur National University, Jodhpur-342 003, India
[2]L.M. College of Pharmacy, Ahmedabad-380 009, India

*Corresponding author: E-mail: devanshu31@gmail.com

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The 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 chemical nature of synthesized compounds have been confirmed by means of IR, NMR and mass data. The synthesized compounds were screened for antitubercular activity. The compounds were subjected to *in vitro* screening by the tube dilution technique employing the human virulent $H_{37}R_V$ strain of *M. tuberculosis* using isoniazid as a reference standard. The results revealed that the test compounds **IIa**, **IIc**, **IId**, **IIe**, exhibits remarkable antitubercular activity against $H_{37}R_V$ strain of *Mycobacterium tuberculosis*. The minimum inhibitory concentration (MIC) values were found in the range of 25 to 42 µg/mL.

Key Words: 4-Thiazolidinones, Isoniazid, *M. tuberculosis*, Minimum inhibitory concentration.

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[1], antifungal[1], antiinflammatory[2], antitubercular[3] and anticonvulsant[4]. 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 antitubercular activity.

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 synthesized a series of some novel 2-(4-substituted phenyl)-3-(4-substituted phenyl)-5-methylthia-zolidin-4-ones. The fluoro, bromo, methoxy, hydroxy, nitro substitutions at *para* position improve antitubercular activity. Therefore it was though worthwhile to synthesize some new 4-thiazolidinone containing compounds and evaluate antitubercular activity.

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 of compounds were recorded using KBr pellets on Perkin-Elmer 337 spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance-300 MHz spectrophotometer using dimethyl sulphoxide as solvent at Indian Institute of Technology, Mumbai. Mass spectra of the synthesized compounds were recorded on Liquid Chromatography Mass Spectrometer as well as C, H, N and S analysis (ThermoFinnigan).

Preparation of N-(4-substituted benzylidine)-4-substituted benzenamine: In a 500 mL round bottom flask equipped with reflux condenser, 4-substituted anilines (5 g, 1 mol) and 4-substituted benzaldehydes (5 g, 1 mol) were dissolved in ethyl alcohol in excess solvent, reflux for 4 h. The reaction mixture were allowed to cool at room temperature. Solid separated by evaporation solvent. The products were recrystallized by using ethanol:ethyl acetate (1:1).

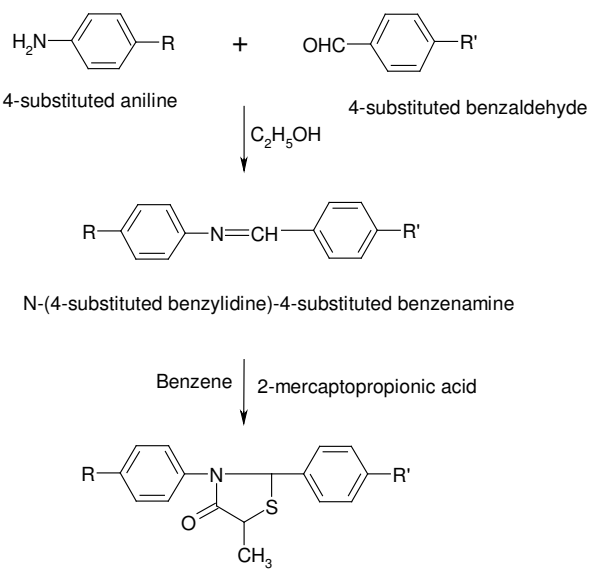
Preparation of 2-(4-substituted phenyl)-3-(4-substituted phenyl)-5-methylthiazolidin-4-one: Compound **I** (0.1 mol) were heated with 2-mercaptopropionic acid (0.2 mol) in

TABLE-1
PHYSICAL CHARACTERISTICS AND ANTITUBERCULAR DATA OF 2-(4-SUBSTITUTED PHENYL)-3-(4-SUBSTITUTED PHENYL)-5-METHYLTHIAZOLIDIN-4-ONES

Compd.	R	R'	m.f.	m.p. (ºC)	Yield (%)	Elemental analysis (%): Calcd. (Found)				$H_{37}R_V$*
						C	H	N	S	
IIa	F	OH	$C_{16}H_{14}NO_2SF$	130-132	69.00	64.31 (64.27)	5.10 (5.06)	4.53 (4.49)	0.81 (0.77)	25
IIb	Br	NO_2	$C_{15}H_{13}N_2O_3SBr$	158-160	70.00	55.75 (55.75)	3.64 (3.60)	4.77 (4.73)	0.82 (0.78)	55
IIc	Br	OH	$C_{16}H_{14}NO_2SBr$	120-122	57.53	71.50 (71.46)	6.39 (6.35)	10.06 (10.02)	0.82 (0.78)	37
IId	F	$N(CH_3)_2$	$C_{18}H_{18}N_2OSF$	123-125	67.00	47.86 (47.82)	2.89 (2.85)	7.88 (7.84)	0.81 (0.77)	30
IIe	Br	OCH_3	$C_{16}H_{16}NO_2SBr$	150-152	61.32	56.71 (56.67)	4.36 (4.32)	3.53 (3.49)	0.001 (0.001)	42
IIf	NO_2	Cl	$C_{16}H_{13}N_2O_3SCl$	126-128	46.35	52.96 (52.92)	4.42 (4.38)	15.81 (15.77)	0.82 (0.78)	52

*$H_{37}R_V$ Strain of *M. tuberculosis* [21 days (µg/mL)]

excess of benzene solvent, reflux for 5 h. The reaction mixture cooled at room temperature. Solid separated by evaporation of solvent. The products were recrystallized by ethanol:dioxane (1:1) (**Scheme-I**). The physical characteristics of compounds **II_a-II_f** were summarized in Table-1.



Scheme-I

Antitubercular screening[5]: The test compounds were subjected to *in vitro* screening by the tube dilution technique employing the human virulent $H_{37}R_V$ strain of *M. tuberculosis*. In this method, Kirchner's medium containing Tween-80 was used.

3-(4-Fluorophenyl)-2-(4-hydroxyphenyl)-5-methylthiazolidin-4-one (IIa): IR (KBr, ν_{max}, cm^{-1}): 3404 (-OH), 1703 (C=O), 3045 (Ar-H), 1308 (C-N). ^1H NMR ($CDCl_3$) δ 6.7-7.0 (m, 8H, Ar-H), δ 1.4 (d, 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 %), R_f: 0.56.

3-(4-Bromophenyl)-5-methyl-2-(4-nitrophenyl)thiazolidin-4-one (IIb): IR (KBr, ν_{max}, cm^{-1}): 1509 (-NO_2), 1703 (C=O), 3079 (Ar-H), 1341 (C-N). ^1H NMR ($CDCl_3$) δ 7.0-7.9 (m, 8H, Ar-H), δ 1.6 (d, 3H, CH-CH_3), δ 5.7 (s, 1H, S-CH-N). LC-MS (m/z, 100 %): 392 ([M^+], 100 %), R_f: 0.51.

3-(4-Bromophenyl)-2-(4-hydroxyphenyl)-5-methylthiazolidin-4-one (IIc): IR (KBr, ν_{max}, cm^{-1}): 3404 (-OH), 1703 (C=O), 3085 (Ar-H); 1325 (C-N). ^1H NMR ($CDCl_3$) δ 7.1-7.9 (m, 8H, Ar-H), δ 1.45 (d, 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 %), R_f: 0.76.

2-(4-(Dimethylamino)phenyl)-3-(4-fluorophenyl)-5-methylthiazolidin-4-one (IId): IR (KBr, ν_{max}, cm^{-1}): 1657 (C=O), 3062 (Ar-H); 1333 (C-N). ^1H NMR ($CDCl_3$) δ 6.8-7.6 (m, 8H, Ar-H), δ 1.4 (d, 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 %), R_f: 65.

3-(4-Bromophenyl)-2-(4-methoxyphenyl)-5-methylthiazolidin-4-one (IIe): IR (KBr, ν_{max}, cm^{-1}): 1698 (C=O), 1315 (C-N), 3007 (Ar-H); 1258 (ether group in ring). ^1H NMR ($CDCl_3$) δ 7.3-7.9 (m, 8H, Ar-H), δ 1.7 (d, 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 %), R_f: 0.54.

2-(4-Chlorophenyl)-5-methyl-3-(4-nitrophenyl)thiazolidin-4-one (IIf): IR (KBr, ν_{max}, cm^{-1}): 1532 (-NO_2), 1698 (C=O), 3078 (Ar-H); 1321 (C-N). ^1H NMR ($CDCl_3$) δ 6.5-7.3 (m, 8H, Ar-H), δ 1.6 (d, 3H, CH-CH_3), δ 5.7 (s, 1H, S-CH-N). LC-MS (m/z, 100 %): 347 ([M^+], 100 %), R_f: 0.71.

The results revealed that the test compounds **IIa**, **IIc**, **IId**, **IIe**, exhibits remarkable antitubercular activity against $H_{37}R_V$ strain of *Mycobacterium tuberculosis*. The minimum inhibitory concentration (MIC) values were found in the range of 25 to 42 mg/mL (Table-1).

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