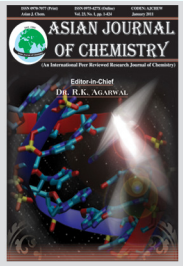
Asian Journal of Chemistry; Vol. 23, No. 3 (2011), 1314-1316

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in



Syntheses of Some Thiazolidin-4-ones as Potential Antimicrobial Agents

FREDDY H. HAVALDAR* and AZAD KUMAR S. SHARMA

Nadkarny-Sacasa Research Laboratory, Department of Chemistry, St. Xavier's College, Mumbai-400 001, India

*Corresponding author: E-mail: drfreddy_11@yahoo.co.in

(*Received*: 13 May 2010; *Accepted*: 10 November 2010) AJC-9294

4-Acetamido-2-methoxybenzoyl hydrazine (**1**) on condensation with different aromatic aldehydes yielded the substituted benzal-(4'-acetamido-2'-methoxybenzoyl)hydrazines (**2a-f**) which on cyclization with thioglycolic acid in presence of anhydrous aluminium chloride as catalyst afforded 2-(substituted phenyl)-3-(4'-acetamido-2'-methoxy benzamido)-5-*H*-thiazolidin-4-ones (**3a-f**). The structures of the newly synthesized compounds have been established by analytical and spectral methods. These compounds have also been screened for their biological activity.

Key Words: Synthesis, Thiazolidin-4-ones, Antibacterial and antifungal activity.

INTRODUCTION

Thiazolidin-4-ones are known to possess antibacterial[1], anticonvulsant[2] and antitubercular[3] activity. The aryl-3-alkyl-4-thiazolidinone[4-7] has been found to be most active as psychomotor anticonvulsants and barbiturate potentiating agents. In view of this, it was considered worthwhile to synthesize some new thiazolidin-4-one derivatives with the objective of screening them for their biological activity.

EXPERIMENTAL

All the melting points were taken in open capillaries and are uncorrected. IR spectra (KBr in cm^{-1}) were recorded on SHIMADZU 8201 PC FTIR spectrophotometer. ^1H NMR spectra were recorded on a Varian 300 MHz NMR spectrophotometer using DMSO-d_6 as solvent and TMS as internal standard (chemical shifts in δ ppm). The purity of the compounds was monitored by thin layer chromatography.

4-Acetamido-2-methoxybenzoyl hydrazine (1): 4-Acetamido-2-methoxy benzoic acid methyl ester (2.23 g, 0.01 mol) and 2 mL of 99 % hydrazine hydrate in 20 cm^3 ethanol was refluxed for about 8 h. The reaction mixture was then allowed to cool to room temperature. The separated white coloured solid was filtered, washed with cold ethanol and crystallized from ethanol, yield 85 %, m.p. 168 ºC; IR (KBr, ν_{max}, cm^{-1}) 3325, 3282 (NH·NH_2), 1684 (C=O amide), 1662 (CO·N), 1613 (C=N), 1585, 1508, 1450 (C=C, aromatic); ^1H NMR (DMSO-d_6) δ 2.3 (s, 3H, N-CO-CH_3), 3.8 (s, 3H, C-OCH_3), 4.3 (s, 2H, NH_2), 6.9-7.3 (m, 3H, ArH), 10.2 (s, 1H, NH-CO-C), 10.9 (s, 1H, CO-NH-N); Anal. calcd. (%) for $C_{10}H_{13}N_3O_3$ requires; C, 53.81; H, 5.87; N, 18.82. Found (%): C, 53.83; H, 5.89; N, 18.84.

Substituted benzal-(4'-acetamido-2'-methoxybenzoyl) hydrazines (2a-f): 4-Acetamido-2-methoxybenzoyl hydrazine **1** (2.23 g, 0.01 mol) was dissolved in 50 cm^3 ethanol containing few drops of glacial acetic acid. The appropriate aromatic aldehyde (0.01 mol) was added and the reaction mixture was refluxed for 3 h, cooled and then poured into crushed ice. The solid obtained was filtered, washed with water and crystallized from ethanol. Other benzal hydrazines were also prepared in similar way.

The characterization and spectral data of compounds (**2a-f**) have been given in Table-1.

2-(Substituted phenyl)-3-(4'-acetamido-2'-methoxy-benzamido)-5-H-thiazolidin-4-ones (3a-f): The benzal hydrazine **2** (0.01 mol) was refluxed with thioglycolic acid (1.40 cm^3, 0.02 mol) in presence of anhydrous aluminium chloride (0.5 g) at 120 ºC for 10-12 h. The reaction mixture was then cooled and triturated with an excess of 10 % sodium bicarbonate solution. The product **3** obtained was filtered, washed several times with water and recrystallized from ethanol. Other thiazolidin-4-ones were prepared in an analogous way. The characterization and spectral data of compounds (**3a-f**) have been given in Table-2.

RESULTS AND DISCUSSION

4-Acetamido-2-methoxybenzoyl hydrazine (**1**) was prepared by hydrazinolysis of 4-acetamido-2-methoxybenzoic acid methyl ester[8]. The acid hydrazide (**1**) was condensed with different aromatic aldehydes in ethanol as solvent to yield

TABLE-1
CHARACTERIZATION DATA OF SUBSTITUTED BENZAL-(4'-ACETAMIDO-2'-METHOXY BENZOYL) HYDRAZINES (**2a-f**)

Compound	Ar	m.p. (ºC)	Yield (%)	m.f.	Analysis (%) N		IR (cm^{-1})
					Calcd.	Found	
2a	Phenyl	223	95	$C_{17}H_{17}N_3O_3$	13.50	13.52	3450 (N-H str.), 1178 (C-O-C), 1028 (C-N str.)
2b	4-Chlorophenyl	280	92	$C_{17}H_{16}N_3O_3Cl$	12.17	12.19	3465 (N-H str.), 1175 (C-O-C), 1031 (C-N str.), 746 (C-Cl str.)
2c	2-Hydroxyphenyl	265	91	$C_{17}H_{17}N_3O_4$	12.84	12.88	3550 (O-H str.), 3466 (N-H str.), 1174 (C-O-C), 1032 (C-N str.)
2d	4-Hydroxyphenyl	280	90	$C_{17}H_{17}N_3O_4$	12.84	12.86	3570 (O-H str.), 3460 (N-H str.), 1174 (C-O-C), 1026 (C-N str.)
2e	4-Hydroxy-3-methoxyphenyl	202	89	$C_{18}H_{19}N_3O_5$	11.76	11.79	3560 (O-H str.), 3463 (N-H str.), 1180 (C-O-C), 1025 (C-N str.)
2f	4-Methoxyphenyl	132	90	$C_{18}H_{19}N_3O_4$	12.31	12.34	3465 (N-H str.), 1174 (C-O-C), 1029 (C-N str.)

TABLE-2
CHARACTERIZATION DATA OF 2-(SUBSTITUTED PHENYL)-3-(4'-ACETAMIDO-2'-METHOXY BENZAMIDO)-5-H THIAZOLIDIN-4-ONES (**3a-f**)

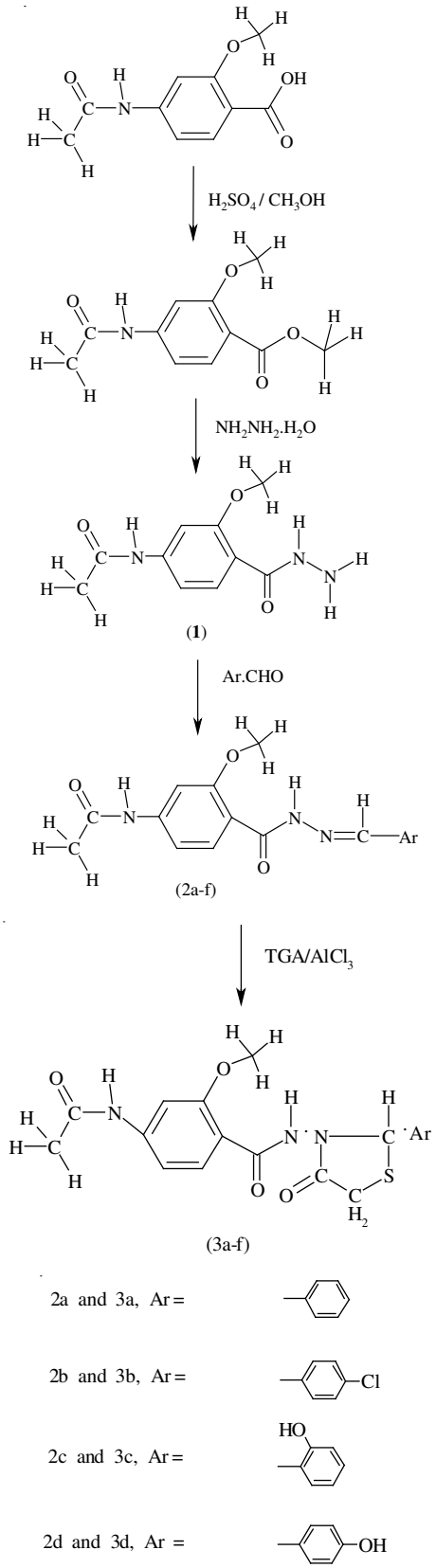
Comp.	Ar	m.p. (ºC)	Yield (%)	m.f.	Analysis (%) N		IR (cm^{-1})	^{1}H NMR
					Calcd.	Found		
3a	Phenyl	115	65	$C_{19}H_{19}N_3O_4S$	10.91	10.95	3450 (N-H str.), 1174 (C-O-C), 1020 (C-N str.), 690 (C-S-C).	2.11 (s, 3H N-C-CH_3), 3.8 (s, 3H –OCH_3), 4.2 (s, 2H –C-CH_2-S), 5.4 (s, 1H –N-CH), 7.1-7.8 (m, 8H ArH), 10.1 (s, 1H, NH-CO-C), 10.85 (s, 1H –CO-NH-N).
3b	4-Chlorophenyl	80	58	$C_{19}H_{18}N_3O_4SCl$	10.02	10.06	3460 (N-H str.), 1178 (C-O-C), 1030 (C-N str.), 740 (C-Cl str.), 696 (C-S-C).	2.10 (s, 3H N-C-CH_3), 3.8 (s, 3H –OCH_3), 4.3 (s, 2H –C-CH_2-S), 5.45 (s, 1H –N-CH), 7.2-7.9 (m, 7H ArH), 10.2 (s, 1H, NH-CO-C), 10.90 (s, 1H –CO-NH-N).
3c	2-Hydroxy-phenyl	110	70	$C_{19}H_{19}N_3O_5S$	10.47	10.51	3575 (O-H str.), 3455 (N-H str.), 1174 (C-O-C), 1030 (C-N str.), 699 (C-S-C).	2.11 (s, 3H N-C-CH_3), 3.85 (s, 3H –OCH_3), 4.35 (s, 2H –C-CH_2-S), 5.5 (s, 1H –N-CH), 7.1-7.8 (m, 7H ArH) 9.3(s, 1H –OH), 10.1 (s, 1H, NH-CO-C), 10.85 (s, 1H –CO-NH-N)
3d	4-Hydroxy-phenyl	130	60	$C_{19}H_{19}N_3O_5S$	10.47	10.50	3558 (O-H str.), 3460 (N-H str.), 1184 (C-O-C), 1030 (C-N str.), 699 (C-S-C).	2.15 (s, 3H N-C-CH_3), 3.8 (s, 3H –OCH_3), 4.4 (s, 2H –C-CH_2-S), 5.5 (s, 1H –N-CH), 7.2-8.0 (m, 7H ArH), 9.4 (s, 1H –OH), 10.1 (s, 1H, NH-CO-C), 10.9 (s, 1H –CO-NH-N)
3e	4-Hydroxy-3-methoxyphenyl	145	62	$C_{20}H_{21}N_3O_6S$	9.74	9.77	3460 (N-H str.), 1182 (C-O-C), 1030 (C-N str.), 698 (C-S-C).	2.2 (s, 3H N-C-CH_3), 3.85 (s, 3H -OCH_3), 3.9 (s, 3H –OCH_3) 4.45 (s, 2H –C-CH_2-S) 5.5 (s, 1H –N-CH), 7.3-8.0 (m, 6H ArH), 9.5 (s, 1H –OH), 10.2 (s, 1H, NH-CO-C), 10.95 (s, 1H -C-NH-N)
3f	4-Methoxy-phenyl	90	69	$C_{20}H_{21}N_3O_5S$	10.11	10.13	3458 (N-H str.), 1182 (C-O-C), 1028 (C-N str.), 695 (C-S-C).	2.11 (s, 3H N-C-CH_3), 3.8 (s, 3H –OCH_3), 3.9 (s, 3H –OCH_3), 4.35 (s, 2H –C-CH_2-S), 5.5 (s, 1H, N-CH), 7.15-7.95 (m, 7H ArH), 10.15 (s, 1H, NH-CO-C), 10.85 (s, 1H –C-NH-N)

TABLE-3
BIOLOGICAL ACTIVITY DATA

Compound / Conc. (mg/mL)	Antibacterial activity								Antifungal activity							
	S. aureus		*E. coli*		*B. subtilis*		*S. typhosa*		*A. niger*		*C. albicans*		*C. neoformans*		*T. paradoxa*	
	2	5	2	5	2	5	2	5	2	5	2	5	2	5	2	5
3a	+	+	+	++	–	+	–	+	+	++	+	+	+	++	–	–
3b	–	–	–	+	–	+	–	–	–	+	–	–	+	+	–	–
3c	–	+	+	++	–	+	–	+	+	+	+	++	–	+	–	+
3d	+	+	+	++	–	+	+	++	+	++	+	+	–	+	–	+
3e	–	–	–	+	+	+	–	+	–	+	–	–	+	+	–	–
3f	–	+	–	+	–	–	–	+	–	+	–	+	+	+	–	+

Inhibition zone diameter in mm: (–) < 11 mm, (+) 11-14 mm, (++) 15-18 mm.

substituted benzal (4'-acetamido-2'-methoxybenzoyl) hydrazines (**2a-f**). The benzal hydrazines (**2a-f**) on cyclization with thioglycolic acid in presence of anhydrous aluminium chloride as catalyst afforded 2-(substituted phenyl)-3-(4'-acetamido-2'-methoxybenzamido)-5-H-thiazolidin-4-ones (**3a-f**), respectively (**Scheme-I**).



Scheme-I

Biological activity

Antibacterial activity: All the newly synthesized thiazolidin-4-ones (**3a-f**) were screened *in vitro* for their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis* and *Salmonella typhosa* by the ditch-plate technique[9] using concentrations of 2 and 5 mg/mL. Nutrient agar was employed as culture media and DMF was used as solvent control for antibacterial activity.

The compound (**3a**) and (**3b**) showed moderate activity against *E. coli* and *Staphylococcus aureus*. The compound (**3d**) exhibited high activity against *E. coli* and moderate activity against *Staphylococcus aureus*. The compounds (**3c**), (**3e**) and (**3f**) possess weak activity against both *E. coli* and *Staphylococcus aureus* (Table-3).

Antifungal acitivity: The compounds (**3a-f**) synthesized were screened for their antifungal activity against *Aspergillus niger*, *Candida albicans*, *Cryptococcus neoformans* and *Thielaviopsis paradoxa* by paper-disc diffusion method[10] at concentrations of 2 and 5 mg/mL. Nutrient agar was employed as culture media and DMF was used as solvent control for antifungal activity.

The compounds (**3a**), (**3c**) and (**3d**) showed marked activity against *Aspergillus niger*, *Candida albicans* and *Cryptococcus neoformans*. The compound (**3b**), (**3e**) and (**3f**) showed moderate activity against *Aspergillus niger*, *Cryptococcus neoformans* and weak activity against *Candida albicans* and *Thielaviopsis p.* (Table-3).

ACKNOWLEDGEMENTS

The authors are thankful to RSIC, IIT, Mumbai for ^{1}H NMR spectra and Dr. (Mrs.) Vivien Amonkar, Head, Department of Microbiology, St. Xavier's College, Mumbai for providing the biological activities.

REFERENCES

1. M.B. Hogle, A.C. Uthale and B.P. Nikam, *Indian J. Chem.*, **30B**, 717 (1991).
2. N.J. Hrib and J.G. Jurcak, 3-[4-(1-Substituted-4-piperazinyl)butyl]-4-thiazolidinone compounds, US Patent 4,933,453 (1991).
3. A.K. Shafei and K.M. Hassan, *Curr. Sci.*, **52**, 633 (1983).
4. H.K. Shukla, R.R. Astik and K.A. Thaker, *J. Indian Chem. Soc.*, **58**, 1182 (1981).
5. N.C. Desai, R.R. Astik and K.A. Thaker, *J. Indian Chem. Soc.*, **50**, 771 (1982).
6. A.R. Surrey and R.A. Cutler, *J. Am. Chem. Soc.*, **76**, 578 (1954).
7. H.D. Troutman and M.N. Long, *J. Am. Chem. Soc.*, **70**, 3436 (1948).
8. D.J. Drain and F.S. Spring, *J. Chem. Soc.*, 1498 (1948).
9. C.H. Collins and P.M. Lyne, Microbiological Methods, Butterworths, London, edn. 3, 424 (1970).
10. H.W. Seeley and P. J. Van Denmark, Microbes in Action, W.H. Freeman and Co., USA (1972).