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Advances in Applied Science Research, 2012, 3 (1):117-122

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ISSN: 0976-8610
CODEN (USA): AASRFC

A facile synthesis and studies of some new 4-thiazolidinones and 5-arylidenes

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ABSTRACT

*Condensation of 4-amino-2,3-dimethyl-1-phenyl-3-pyrazoline-5-one with different aromatic and heterocyclic aldehydes in dry toluene give schiff bases **3(a-g)**, which on reaction with thioglycolic acid and thiolactic acid in dry toluene give the corresponding 2,3-disubstituted-4-thiazolidinones **4(a-g)** and 2,3-disubstituted-5-methyl-4-thiazolidinones **5(a-g)**. The methylene carbon atom at the position 5 of 4-thiazolidinone possesses nucleophilic activity. The Knoevenagel reaction of methylene group of 4-thiazolidinone has been widely attempted. Further 2,3-disubstituted-4-thiazolidinones **4(a-g)** on condensation with 4-methoxybenzaldehyde (Knoevenagel reaction) in alcohol in the presence of sodium- ethoxide give its corresponding 2,3-disubstituted-5-arylidene **6(a-g)** derivatives. Structures of newly synthesised compounds were established on the basis of their elemental analysis, IR and ^{1}H NMR spectral data. Antibacterial activity (minimum inhibitory concentration MIC) against Gram-positive (S. aureus MTCC 96 and S. pyogeneus MTCC 442) and Gram-negative (P. aeruginosa MTCC 1688 and E. coli MTCC 443) bacteria, as well as antifungal activity (MIC) against C. albicans MTCC 227, A. niger MTCC 282 and A. clavatus MTCC 1323 were determined by broth dilution method.*

Keywords 4- Thiazolidinones, Thioglycolic acid, Thiolactic acid, Arylidines, Microbial studies.

INTRODUCTION

Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring. 4-Thiazolidinones [1] have attracted considerable attention as they are endowed with wide range of pharmaceutical activities. The nucleus is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities. The presence of N-C-S linkage in the compounds has been shown to have antimicrobial [2] and anti-HIV [3,4] activities etc… . Some 4-thiazolidinones have been assessed for their antifungal [5], antitubercular [6,7], hypnotic [8,9] and antioxidant [10] activities etc…. The 5-arylidene derivatives of 4-thiazolidinones are also well known for their versatile pharmacological activities [11-13]. The presence of certain groups such as hydroxy, methoxy, thio and chloro in the phenyl ring has been reported to increase the activity of the parent compounds. The 5-arylidene derivatives are known to possess analgesic [14], anticonvulsant [15], antiviral [16], anti-inflammatory [17] and anticancer [18] activities etc… . In a continuation of our work on 4-thiazolidinones [19-21], herein we report some 2, 3-disubstituted-4-thiazolidinones **4(a-g)**, 2, 3-disubstituted-5-methyl-4-thiazolidinones **5(a-g)** and 2, 3-disubstituted-5-arylidene **6(a-g)**. The synthesised compounds were ascertained from spectral and physiochemical analysis. Results of IR and ^{1}H NMR analysis confirmed formation of the desired products.

MATERIALS AND METHODS

All melting points were determined in an open capillary and are uncorrected. The IR spectra were recorded on a FTIR - 8400 spectrophotometer. ^{1}H NMR spectra on a Bruker Avance DPX 400 MHz spectrometer with DMSO as a solvent and tetramethylsilane (TMS) as internal standard. The chemical shifts are expressed in parts per million (ppm) downfield from the internal standard and signals are quoted as *s* (singlet), *d* (doublet) and *m* (multiplate). Thin Layer Chromatography (TLC) analytical separation was conducted with Silica Gel 60 F-254 (Merck) plates of 0.25mm thickness eluted with toluene : acetone (10 : 4 v/v) and visualized with UV (254 nm) or iodine to check the purity of the synthesised compounds. The synthesised compounds were screened for their antimicrobial activity. The synthesised compounds were ascertained from spectral and physiochemical analysis. Results of IR and ^{1}H NMR analysis confirmed formation of the desired products.

Schiff bases were prepared by known method [22].

Preparation of 2-(2″, 5″-dimethoxyphenyl)-3-(2', 3'-dimethyl-1'-phenyl -3'-pyrazoline-5'-one-4'-yl)-4-thiazolidinones (4a)

Compound **(3a)** (0.01 mole) and thioglycolic acid (0.012 mole, 1.104g) in dry toluene (80 ml) was refluxed on water bath for 10-12 hours using Dean-Stark water separator. The progress of the reaction was monitored on TLC plate. Excess of toluene was then distilled off and the resulting viscous liquid was treated with saturated $NaHCO_3$ solution to remove unreacted thioglycolic acid. The product separated out was washed with water, dried and recrystallised from alcohol.

Similarly, the remaining compounds **(4b-g)** were prepared by this method. Their physical data are given in **Table-1.**
Compound (4a) IR (KBr,cm^{-1}) : 3068 (=CH str.), 2971 (C-H str.), 1690 (C=O str.), 1241 (C-O-C str.), 827 (C-H bending), 641 (C-S-C str.) ; ^{1}H NMR ($CDCl_3$, δ, ppm): 1.89 (3H, *s*, N-CH_3), 2.91 (3H, *s*, C-CH_3), 3.71 (3H, *s*, o-OCH_3), 3.79 (3H, *s*, m-OCH_3), 6.2 (1H, *s*, -CH-Ar), 3.96 (2H, *q*, -CH_2-), 6.5 – 7.7 (8H, *m*, Ar-H).

Preparation of 2-(2″, 5″-dimethoxyphenyl)-3-(2', 3'-dimethyl-1'-phenyl-3'-pyrazoline-5'-one-4'-yl) -5-methyl-4-thiazolidinones (5a)

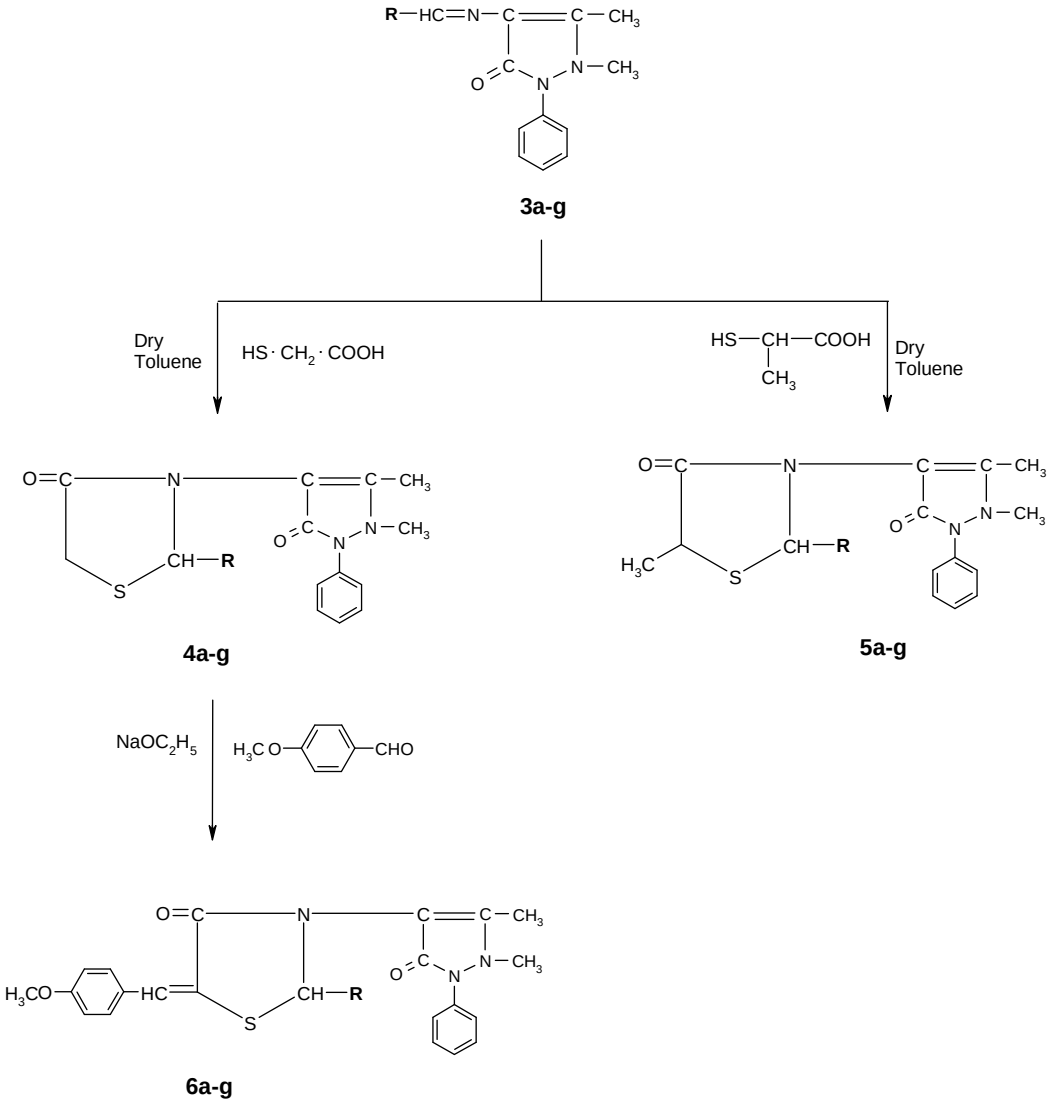
Compound (3a) (0.01 mole) and thiolactic acid (0.012 mole, 1.272g) in dry toluene (80 ml) was refluxed on water bath using Dean-Stark water separator for 10-12 hours. The progress of the reaction was monitored on TLC plate. Excess of toluene was then distilled off and the resulting viscous liquid was treated with saturated $NaHCO_3$ solution to remove unreacted thiolactic acid. The product separated out was washed with water, dried and recrystallised from alcohol.

Similarly, the remaining compounds **(5b-g)** were prepared by this method. Their physical data are given in **Table-1.**
Compound (5a) IR (KBr,cm^{-1}) : 3025 (=CH str.), 2976 (C-H str.), 1695 (C=O str.), 1245 (C-O-C str.), 812 (C-H bending), 637 (C-S-C str.) ; ^{1}H NMR ($CDCl_3$, δ, ppm): 1.91 (3H, *s*, N-CH_3), 2.1 (3H, *d*, CH-C<u>H</u>$_3$), 3.1 (3H, *s*, C-CH_3), 3.49 (3H, *s*, o-OCH_3), 3.6 (3H, *s*, m-OCH_3), 6.4 (1H, *s*, -CH-Ar), 3.96 (1H, *q*, -C<u>H</u>- CH_3), 6.6 – 7.7 (8H, *m*, Ar-H).

Preparation of 2-(2″, 5″-dimethoxyphenyl)-3-(2', 3'-dimethyl-1'-phenyl-3'- pyrazoline -5'- one -4'- yl) -5- [(4'-methoxy) benzylidene]-4-thiazolidinones (6a)

Compound **(4a)** (0.01 mole) was dissolved in 40 ml alcohol. Then sodium ethoxide (0.01 mole, 0.82 g) and 4-methoxybenzaldehyde (0.01 mole, 1.36g) were added in it. The reaction mixture was then refluxed for 6 hours. The progress of the reaction was monitored on TLC plate. After completion, the reaction mixture was cooled and poured into crushed ice, the product separated out was filtered, washed with water, dried and recrystallised from alcohol.

Similarly, the remaining compounds **(6b-g)** were prepared by this method. Their physical data are given in **Table-1**.
Compound (6a) IR (KBr,cm^{-1}) : 3033 (=CH str.), 2976 (C-H str.), 1691 (C=O str.), 1248 (C-O-C str.), 813 (C-H bending), 635 (C-S-C str.) ; ^{1}H NMR ($CDCl_3$, δ, ppm): 1.93 (3H, *s*, N-CH_3), 2.1 (3H, *s*, C-CH_3), 3.2 (3H, *s*, o-OCH_3), 3.4 (3H, *s*, m-OCH_3), 3.6 (3H, *s*, p-OCH_3), 6.21 (1H, *s*, -CH-Ar), 7.9 (1H, *s*, Ar-C<u>H</u>=), 6.6 – 7.7 (12H, *m*, Ar-<u>H</u>).



Scheme

RESULTS AND DISCUSSION

Minimum inhibitory concentration (MIC) of all the synthesised compounds have been screened by broth dilution method [23] against four different strains, viz. two Gram positive bacteria (*S. aureus* MTCC 96 and *S. pyogenes* MTCC 442) and two Gram negative bacteria (*E.coli* MTCC 443 and *P. aeruginosa* MTCC 1688) and compared with standard drug : Ampicillin. Antifungal activity against *C. albicans* MTCC 227, *A. niger* MTCC 282 and *A. clavatus* MTCC 1323 organisms was determined by same method and compared with standard drug : Griseofulvin.

Antibacterial activity

In Gram positive bacterial strains compounds **4b, 4d, 4f, 5a, 5f** and **6f** showed good to very good activity (25 – 150 µg/ml) against *S. aureus* ; where as compounds **5g** and **6e** showed good activity (62.5 – 100 µg/ml) against *S. pyogenes* compared with Ampicillin. In Gram negative bacterial strains : The result shows that compounds **4a, 5d, 5e, 5f, 6b, 6c** and **6e** showed good activity (25 – 125 µg/ml) against *E. coli* ; compounds **6b, 6c** and **6e** showed good activity (50 – 100 µg/ml) against *P. aeruginosa*. All others compounds show moderately active or less active against all bacterial strains.

Table -1 Characterization data of compounds (4a-g), (5a-g) and (6a-g)

Comps	R	M. F.	m.p. °C	Elemental Analysis		
				% C Found (Calcd)	% N Found (Calcd)	% H Found (Calcd)
4a	2,5-Dimethoxyphenyl	$C_{22}H_{23}N_3O_4S$	183	62.08 (62.10)	9.86 (9.88)	5.41 (5.45)
4b	2,4-Dichlorophenyl	$C_{20}H_{17}Cl_2N_3O_2S$	152	55.29 (55.31)	9.65 (9.67)	3.93 (3.95)
4c	4-Fluorophenyl	$C_{20}H_{18}FN_3O_2S$	139	62.63 (62 .65)	10.95 (10.96)	4.70 (4.73)
4d	2-Hydroxyphenyl	$C_{20}H_{19}N_3O_3S$	165	62.96 (62.98)	11.00 (11.02)	5.00 (5.02)
4e	4-N,N-diethylamino-2-hydroxyphenyl	$C_{24}H_{28}N_4O_3S$	220	63.67 (63.69)	12.35 (12.38)	6.21 (6.24)
4f	3-Bromo-4-hydroxy-5-methoxyphenyl	$C_{21}H_{20}BrN_3O_4S$	141	51.42 (51.44)	8.54 (8.57)	4.09 (4.11)
4g	6-Quinoline	$C_{23}H_{20}N_4O_2S$	143	66.30 (66.33)	13.42 (13.45)	4.81 (4.84)
5a	2,5-Dimethoxyphenyl	$C_{23}H_{25}N_3O_4S$	185	62.83 (62.85)	9.55 (9.56)	5.70 (5.73)
5b	2,4-Dichlorophenyl	$C_{21}H_{19}Cl_2N_3O_2S$	179	56.24 (56.26)	9.36 (9.37)	4.25 (4.27)
5c	4-Fluorophenyl	$C_{21}H_{20}FN_3O_2S$	175	63.44 (63.46)	10.56 (10.57)	5.05 (5.07)
5d	2-Hydroxyphenyl	$C_{21}H_{21}N_3O_3S$	180	63.76 (63.78)	10.60 (10.62)	5.30 (5.35)
5e	4-N,N-diethylamino-2-hydroxyphenyl	$C_{25}H_{30}N_4O_3S$	215	64.30 (64.35)	12.00 (12.01)	6.45 (6.48)
5f	3-Bromo-4-hydroxy-5-methoxyphenyl	$C_{22}H_{22}BrN_3O_4S$	218	52.36 (52.39)	8.31 (8.33)	4.35 (4.40)
5g	6-Quinoline	$C_{24}H_{22}N_4O_2S$	151	66.94 (66.96)	13.00 (13.01)	5.11 (5.15)
6a	2,5-Dimethoxyphenyl	$C_{30}H_{29}N_3O_5S$	118	66.25 (66.28)	7.69 (7.73)	5.36 (5.38)
6b	2,4-Dichlorophenyl	$C_{28}H_{23}Cl_2N_3O_3S$	151	60.85 (60.87)	7.59 (7.61)	4.16 (4.20)
6c	4-Fluorophenyl	$C_{28}H_{24}FN_3O_3S$	265	67.01 (67.05)	8.36 (8.38)	4.79 (4.82)
6d	2-Hydroxyphenyl	$C_{28}H_{25}N_3O_4S$	122	67.30 (67.32)	8.38 (8.41)	5.00 (5.04)
6e	4-N,N-diethylamino-2-hydroxyphenyl	$C_{32}H_{34}N_4O_4S$	270	67.32 (67.35)	9.80 (9.82)	6.00 (6.01)
6f	3-Bromo-4-hydroxy-5-methoxyphenyl	$C_{29}H_{26}BrN_3O_5S$	204	57.21 (57.24)	6.89 (6.91)	4.29 (4.31)
6g	6-Quinoline	$C_{31}H_{26}N_4O_3S$	120	69.61 (69.64)	10.45 (10.48)	4.88 (4.90)

Antifungal activity

From the screening results, compound **5b** showed very good activity against *C. albicans*, while Compounds **4a, 4e, 4f, 5c, 5d, 5e, 6a, 6d** and **6f** showed good activity against *C. albicans* compared with Griseofulvin. Rest of the compounds show moderately active or less active against all bacterial strains.

CONCLUSION

From the results of antibacterial and antifungal activity; it can be concluded that the compounds bearing -OH, -OCH_3, -F and -Br group are more potent than the remaining compounds. They showed comparatively good antibacterial as well as antifungal activity.

Table 2 – Antibacterial and antifungal activity data of compounds 4(a-g), 5(a-g) and 6(a-g)

Compounds	Minimal bactericidal concentration µg/ml				Minimal fungicidal concentration µg/ml		
	Gram negative		Gram positive				
	E. coli MTCC-443	*P. aerug* MTCC-1688	*S. aureus* MTCC-96	*S. pyogenus* MTCC-442	*C. albicans* MTCC-227	*A. niger* MTCC-282	*A. clavatus* MTCC-1323
4a	100	200	200	500	500	>1000	>1000
4b	250	200	125	125	1000	1000	1000
4c	200	250	250	200	>1000	500	500
4d	250	200	125	200	>1000	500	500
4e	250	250	200	250	500	>1000	>1000
4f	200	250	125	125	500	>1000	>1000
4g	250	500	250	250	1000	500	500
5a	500	200	125	200	1000	>1000	>1000
5b	500	250	250	500	250	>1000	>1000
5c	500	125	250	250	500	>1000	>1000
5d	100	250	200	250	500	>1000	>1000
5e	100	125	200	125	500	>1000	>1000
5f	125	200	62.5	125	>1000	1000	1000
5g	200	200	200	100	>1000	250	250
6a	250	250	200	250	500	1000	>1000
6b	100	100	500	250	1000	>1000	>1000
6c	100	100	500	500	1000	>1000	>1000
6d	250	200	500	200	500	500	500
6e	100	100	200	100	1000	>1000	>1000
6f	500	500	125	250	500	>1000	>1000
6g	200	250	250	250	>1000	>1000	>1000
Ampicillin	100	100	250	100	-	-	-
Griseofulvin	-	-	-		500	100	100

Acknowledgement
We are grateful to B. K. M. Science College, Valsad for providing research facilities, Atul Ltd. (Atul) for the IR spectral analysis, RSIC Punjab University for the ^{1}H NMR spectral analysis and D. Rajani, Microcare Laboratory, Surat, for antimicrobial activity screening.

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