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Synthesis of Schiff base and 4-oxo-thiazolidines of 5-bromo furan-2-carbohydrzide and their derivatives as an antimicrobial agent

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ABSTRACT

*A series of Schiff bases **(2a-f)** have been prepared by the condensation of 5-bromofuran-2-carboxyhydrazide **(1)** with different aromatic and heterocyclic aldehydes. The synthesis of various 2-(substituted phenyl/quinolin 2-yl/6-methoxy naphthalen 2-yl)-3-(5'-bromofuran-2'-carboxamido) – thiazolidine-4-ones **(3a-f)** by cyclocondensation reaction between schiff bases **(2a-f)** and thioglycolic acid. Cyclocondensation of Schiff bases **(2a-f)** with thiolactic acid resulted 2-(susbstituted phenyl)-3-(5'-bromofuran-2'-carboxamido)–5-methyl thiazolidine - 4 - ones **(4a-f)**. The structures of all the synthesised compounds were confirmed by their elemental analysis and IR, ^{1}H NMR spectral data. All the synthesised compounds have been screened for their antimicrobial activity.*

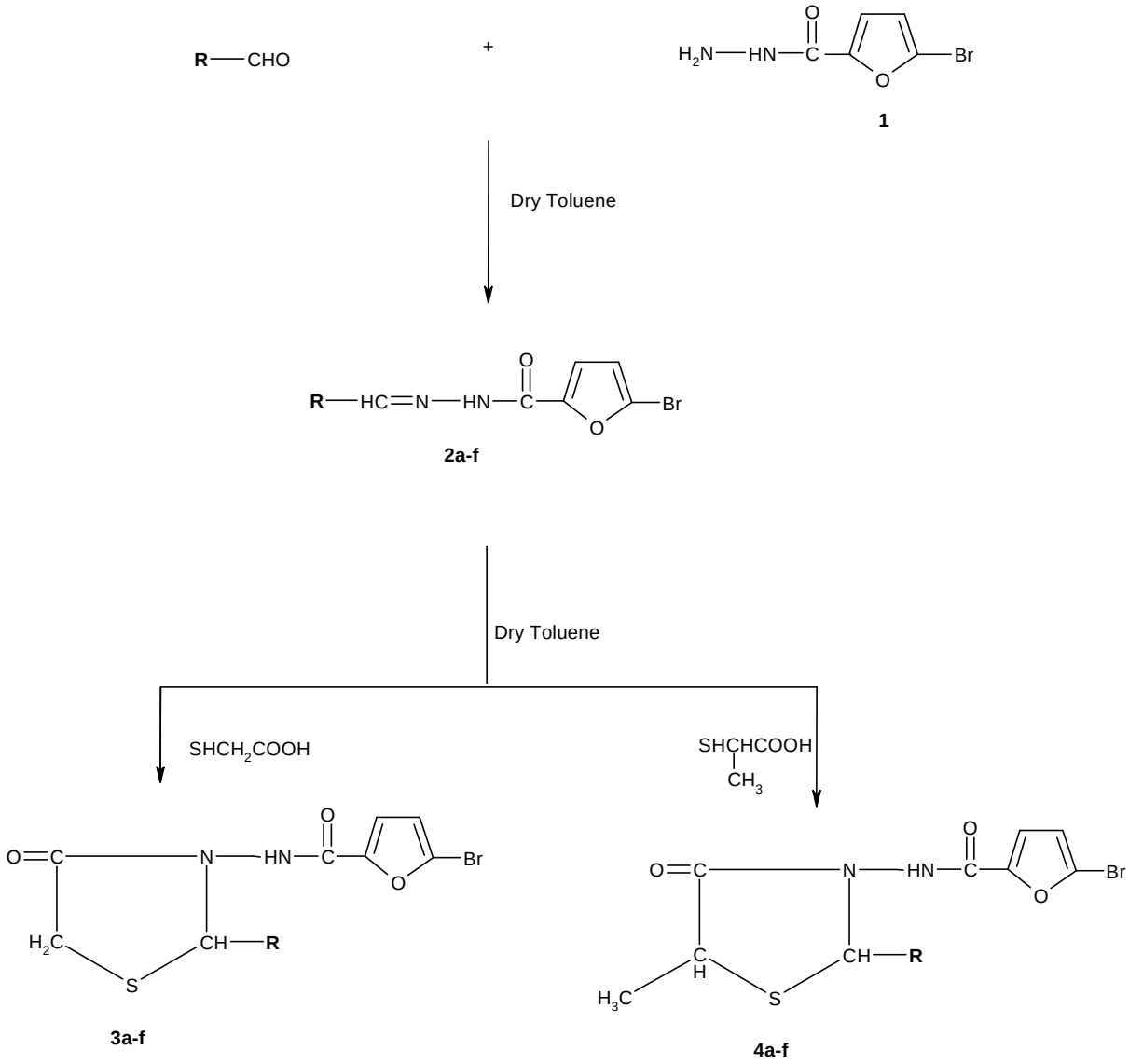
Keywords: Hydrazones, 4-Oxo-thiazolidines, Thioglycolic acid, Thiolactic acid, Spectral data, Antimicrobial activity.

INTRODUCTION

The quest for a more reliable and suitable drug is always fascinating and challenging. A number of drugs containing simple heterocycle or a combination of different heterocyclic moieties have been in use these days. Hydrazones have gained more importance because of their physiological and pharmacological activities such as antitubecular [1], antifungal [2], anticancer [3] etc… activities. They have been frequently employed for medicinal use. Literature [4] reveals that 4-oxo-thiazolidines have exihibited promising biological and pharmacological activities such as anticonvulsant [5], antitumor [6], antibacterial [7, 8], antitubecular [9], hypnotic [10], anticancer [11], cardivascular [12], antioxidant [13] activities etc… . etc.. activities. 4-Oxo-thiazolidinones are synthesized either by cyclisation of acyclic compounds or by interconversation among appropriately substituted thiazolidine derivatives. Different methods for the preparation of 4-oxo-thiazolidines have been reported [14-15]. In continuation of our works on 4-oxo-thiazolidines derivatives [16-19], we have undertaken the synthesis of 4-oxo-thiazolidines of type **(3a-f)** by the condensation of Schiff-bases **(2a-f)** with thioglycolic acid. Cyclocondensation of schiff-bases **(2a-f)** with thiolactic yielded 4-oxo-thiazolidines of type **(4a-f)**. All the synthesised compounds were confirmed on the basis of their spectral data and physical data.

MATERIALS AND MATHODS

All the melting points were determined in an open capillary and are uncorrected. The IR spectra were recorded on Perkin-Elmer spectrum BX series FT-IR spectrophotometer. ^{1}H NMR spectra on a Varian Gemini 400 MHz spectrometer with $CDCl_3$ as a solvent and TMS as internal reference. The chemical shifts are expressed in part 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 visualized with UV (254nm) or iodine to check the purity of the synthesised compounds. Elemental analyses were carried out on a Perkin-Elmer series ii 2400 equipment.



SCHEME - 1

Preparation of N-(3',4'-methoxybenzylidene)-5–bromofuran-2-carbonyl hydrazones (2a).

5-Bromofuran-2-carbohydrazide **(1)** (0.01 mol) and 2,3- dimethoxybenzaldehyde (0.01 mol) in dry toluene (50 mL) were refluxed on water bath using Dean-Stark water separator for 4-5 hours. The progress of the reaction was monitored on TLC plate. Excess of toluene was then distilled off and the product separated out was recrystallized from alcohol to give **2(a).**

Similarly, the remaining compounds **(2b-f)** were prepared by this method. Their physical data are given in **Table-1.**

Compoud (2a) : IR (KBr) cm^{-1}; 1660 (>C=O, -CONH str), 1570 (-N=CH str), 1246 (C-O-C str), 625 (C-Br str); ^{1}H NMR (DMSO) δ ppm ; 3.40 (3H, *s*, m-OCH_3), 3.74 (3H, *s*, p-OCH_3), 6.30-7.81 (5H, *m*, Ar-H and –CH of furan ring), 8.1(1H, *s*, N=CH), 9.3 (1H, s, -CONH).

Preparation of 2-(3',4'-dimethoxyphenyl)-3-(5'-bromofuran-2'-carboxamido)– thiazolidine- 4 - one (3a)

Compound **(2a)** (0.01 mole) and thioglycolic acid (0.012 mole, 1.104g) in dry toluene (80 ml) were 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 **(3b-f)** were prepared by this method. Their physical data are given in **Table-1.**

Compound (3a) IR (KBr) cm^{-1}; 1673 (>C=O, -CONH str), 1680 (>C=O, thiazolidine ring), 1249 (C-O-C str), 709 (C-S-C str), 620 (C-Br str); ^1H NMR ($CDCl_3$) δ ppm; 3.5-3.7 (2H, *q*, $-CH_2$), 3.85 (3H, *s*, m-OCH_3), 3.92 (3H, *s*, p-OCH_3), 5.9 (1H, s, -CH-Ar), 6.45 -7.20 (5H, m, Ar-H and -CH furan ring), 8.0 (1H, s, -CONH).

Preparation of 2-(3',4'-dimethoxyphenyl)-3-(5'-bromofuran-2'-carboxamido)– 5- methyl-thiazolidine-4 - ones (4a)

Compound **(2a)** (0.01 mole) and thioglycolic acid (0.012 mole, 1.104g) in dry toluene (80 ml) were 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-f)** were prepared by this method. Their physical data are given in **Table-1.**

Compound (4a) IR (KBr) cm^{-1}; 1673 (>C=O, -CONH str), 1685 (>C=O, thiazolidine ring), 1249 (C-O-C str), 709 (C-S-C str), 620 (C-Br str); ^1H NMR ($CDCl_3$) δ ppm; 1.63 (3H, *d*, $-CH_3$), 3.72 (3H, *s*, m-OCH_3), 3.89 (3H, *s*, p-OCH_3), 5.89 (1H, s, -CH-Ar), 6.35 -7.60 (5H, m, Ar-H and -CH furan ring), 8.2 (1H, s, -CONH).

RESULTS AND DISCUSSION

Minimum inhibitory concentration (MIC) of all the synthesised compounds have been screened by Broth dilution method [20] against four different strains, viz. Gram positive bacteria (*S. aureus* MTCC 96 and *S. pyogenes* MTCC 442) and 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 **2a, 2d, 2e, 3c, 3e, 3f** and **4d** showed good to very good activity (25 – 150 µg/ml) against *S. aureus* ; where as compound **3e, 3f** and **4d** showed very good activity (62.5 – 100 µg/ml) against *S. pyogenes* compared with Ampicillin. In Gram negative bacterial strains : The result shows that compounds **2d, 2e, 3a, 3b, 3d, 4b, 4c** and **4f** showed very good activity (25 – 125 µg/ml) against *E. coli* ; compounds **2f, 4b** and **4c** showed good activity (50 – 100 µg/ml) against *P. aeruginosa*. All others compounds show moderately active or less active against all bacterial strains.

ANTIFUNGAL ACTIVITY

From the screening results **(Table – 2)**, compounds **3b, 4c** and **4c** showed very good activity against *C. albicans*, while Compounds **2b, 2d, 2e, 3d** and **4a** showed good activity against *C. albicans* compared with Griseofulvin. Rest of the compounds show moderately active or less active against all bacterial strains.

Table -1 Characterisation data of compounds (2a-f), (3a-f) and (4a-f)

Comps	R	M. F.	m.p. °C	Elemental Analysis		
				% C Found (Calcd)	% N Found (Calcd)	% H Found (Calcd)
2a	3,4-Dimethoxyphenyl	$C_{14}H_{13}BrN_2O_4$	210	47.61 (47.60)	7.93 (7.90)	3.71 (3.69)
2b	4-Hydroxy-3-methoxyphenyl	$C_{13}H_{11}BrN_2O_4$	255	63.47 (63.48)	14.30 (14.33)	3.75 (3.78)
2c	4-Hydroxy-3-ethoxyphenyl	$C_{14}H_{13}BrN_2O_4$	182	47.61 (47.58)	7.93 (7.91)	3.71 (3.69)
2d	2-Hydroxyphenyl	$C_{12}H_9BrN_2O_3$	190	46.63 (47.61)	9.06 (9.03)	2.93 (2.91)
2e	4-Benzyloxy-3-methoxypheyl	$C_{20}H_{17}BrN_2O_4$	149	55.96 (55.94)	6.53 (6.50)	3.99 (3.97)
2f	6-Methoxy- naphthalene	$C_{17}H_{13}BrN_2O_3$	188	54.71 (54.69)	7.51 (7.50)	3.51 (3.49)
3a	3,4-Dimethoxyphenyl	$C_{16}H_{15}BrN_2O_5S$	175	44.98 (44.97)	6.56 (6.53)	3.54 (3.51)
3b	4-Hydroxy-3-methoxyphenyl	$C_{15}H_{13}BrN_2O_5S$	170	43.60 (43.58)	6.78 (6.76)	3.17 (3.15)
3c	4-Hydroxy-3-ethoxyphenyl	$C_{16}H_{15}BrN_2O_5S$	195	44.98 (44.97)	6.56 (6.54)	3.54 (3.55)
3d	2-Hydroxyphenyl	$C_{14}H_{11}BrN_2O_4S$	119	43.88 (43.86)	7.31 (7.29)	2.89 (2.87)
3e	4-Benzyloxy-3-methoxypheyl	$C_{22}H_{19}BrN_2O_5S$	124	52.49 (52.46)	5.57 (5.55)	3.80 (3.78)
3f	6-Methoxy- naphthalene	$C_{19}H_{15}BrN_2O_4S$	110	51.02 (51.00)	6.26 (6.23)	3.38 (3.40)
4a	3,4-Dimethoxyphenyl	$C_{17}H_{17}BrN_2O_5S$	112	46.27 (46.25)	6.35 (6.33)	3.38 (3.37)
4b	4-Hydroxy-3-methoxyphenyl	$C_{16}H_{15}BrN_2O_5S$	130	44.98 (44.96)	6.56 (6.54)	3.54 (3.52)
4c	4-Hydroxy-3-ethoxyphenyl	$C_{17}H_{17}BrN_2O_5S$	210	46.27 (46.24)	6.35 (6.34)	3.38 (3.35)
4d	2-Hydroxyphenyl	$C_{15}H_{13}BrN_2O_4S$	150	45.35 (43.33)	7.05 (7.02)	3.30 (3.28)
4e	4-Benzyloxy-3-methoxypheyl	$C_{23}H_{21}BrN_2O_6S$	80	51.79 (51.77)	5.25 (5.23)	3.97 (3.95)
4f	6-Methoxy- nephthalene	$C_{20}H_{17}BrN_2O_5S$	180	50.32 (50.30)	5.87 (5.85)	3.59 (3.57)

Table 2 – Antibacterial and antifungal activity data of compounds (2a-f), (3a-f) and (4a-f).

Compound	Minimal bactericidal concentration µg/ml				Minimal fungicidal concentration µg/ml		
	Gram positive		Gram negative				
	***S. aureus* MTCC 96**	***S. Pyogenus* MTCC 442**	***E. coli* MTCC 443**	***P. aerug* MTCC 1688**	***C. albicans* MTCC 227**	***A. niger* MTCC 282**	***A. clavatus* MTCC 1323**
2a	125	125	200	125	1000	>1000	>1000
2b	500	500	250	200	500	1000	1000
2c	200	200	250	250	>1000	500	1000
2d	62.5	250	62.5	125	500	1000	1000
2e	125	250	100	200	500	1000	1000
2f	250	500	200	62.5	>1000	250	500
3a	250	250	125	250	>1000	1000	1000
3b	200	200	100	200	250	1000	>1000
3c	120	200	200	200	1000	250	500
3d	200	250	100	125	500	1000	1000
3e	100	100	500	500	1000	>1000	>1000
3f	62.5	100	250	250	>1000	1000	1000
4a	250	250	200	200	500	1000	1000
4b	250	200	125	62.5	1000	500	500
4c	200	200	100	100	250	500	500
4d	62.5	100	200	250	1000	200	500
4e	500	500	250	250	250	500	1000
4f	200	200	100	200	>1000	>1000	>1000
Ampicillin	250	100	100	100	-	-	-
Griseofulvin	-	-	-		500	100	100

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