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A convenient synthesis of some new 4-thiazolidinones and 2-azetidinones as potential antimicrobial agents

Kishor Kapadia, Hiral Patel, Yogesh Prajapati, Pankit Solankee, Sejal Solankee, Anjani Solankee*

Department of Chemistry, B.K.M.Science College, Valsad-396001, (INDIA)

E-mail: dranjani_solankee@yahoo.com

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ABSTRACT

A series of 2-(substituted phenyl)-3-(5'-methyl thiazole)-4-thiazolidinones **(4)**, 2-(substituted phenyl)-3-(5'-methyl thiazole)-5-methyl-4-thiazolidinones **(5)** and 4-(substituted phenyl)-3-chloro-1-yl-(5'-methyl thiazole)-2-azetidinones **(6)** were prepared by cyclocondensation of thioglycolic acid, thiolactic acid and chloroacetyl chloride in presence of triethyl amine with different Schiffbases, which in turn were prepared by the 2-amino-5-methylthiazole with different substituted aromatic aldehydes **(2)**. The structures of newly synthesized compounds have been characterized on the basis of elemental analysis, IR and ^{1}H NMR spectra. All the synthesised compounds have been screened for their antimicrobial activity.

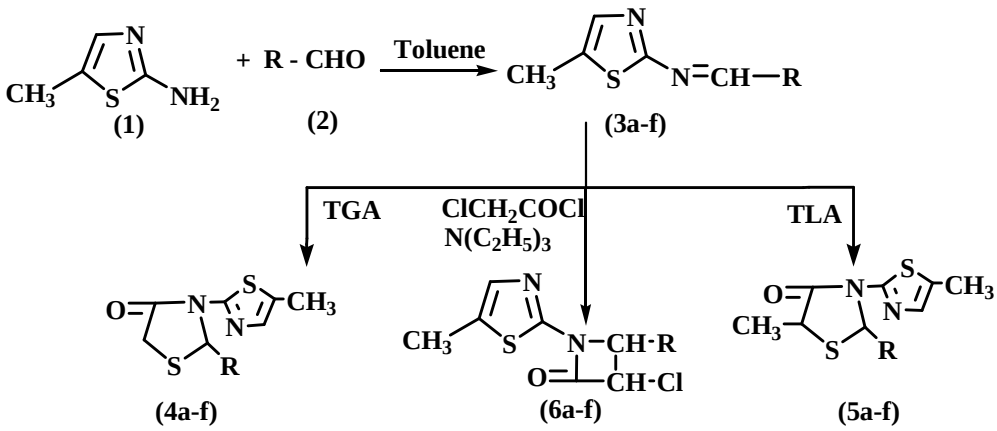
KEYWORDS

4-Thiazolidinones;
2-Azetidinones;
Antimicrobial activity.

INTRODUCTION

The β-lactams are 4-membered cyclic system. The first member was synthesized by Staudinger[1] in 1907. The β-lactams as a class acquired importance since the discovery of penicillin which contains β-lactam unit as an essential structural feature of its molecule. Moreover much interest has been focused on biological activities of thiazole derivatives[2-4]. In search of more biologically effective agent and industrial utility led to explore a variety of chemical entities with biological properties. Led by these considerations, synthesis of 2-azetidinones and 4-thiazolidinones bearing thiazole nucleus has been undertaken in order to study biodynamic behaviour of the compounds. Thiazoles[5] are also shown to possess various biological activities such as anti-inflammatory[6], antitubercular[7] and antimicrobial[8]. Literature survey reveals that various 4-thiazolidinones[9] and 2-azetidinones[10] have attracted considerable attention as they are also endowed with wide range of pharmaceutical activities. 4-Thiazolidinones have been assessed for their antimicrobial[11], antitubercular[12], anticancer[13], antifungal[14] and insecticidal[15] activities. 2-Azetidinones have been extensively explored for their antimicrobial[16], antitubercular[17], anticancer[18] and anti-inflammatory[19] activities.

2-amino-5-methyl thiazole **(1)** on condensation with different substituted aromatic aldehydes **(2)** yielded Schiff bases **(3)**. Compound **(3)** on cyclocondensation with thioglycolic acid and thiolactic acid and chloroacetyl chloride in presence of triethylamine afforded 2-(substituted phenyl)-3-(5'-methyl thiazole)-



SCHEME

TABLE 1 : Physical and analytical data of compounds (3a-f), (4a-f), (5a-f) and (6a-f)

No.	R	M.P. (°C)	Yield (%)	Molecular formula	Found/(calcd.)%		
					C	H	N
3a	3-Nitrophenyl	129	83	$C_{11}H_9N_3O_2S$	53.42(53.44)	3.67(3.64)	17.03(17.00)
3b	4-Nitrophenyl	148	81	$C_{11}H_9N_3O_2S$	53.47(53.44)	3.66(3.64)	17.02(17.00)
3c	3,4,5-Trimethoxyphenyl	Limpid	84	$C_{14}H_{16}N_2O_3S$	57.56(57.53)	5.50(5.48)	9.57(9.59)
3d	3-Bromophenyl	94	85	$C_{11}H_9BrN_2S$	46.99(46.98)	3.18(3.20)	9.93(9.96)
3e	4-Fluorophenyl	87	88	$C_{11}H_9FN_2S$	60.03(60.00)	4.10(4.09)	12.74(12.73)
3f	3-Methoxyphenyl	105	85	$C_{12}H_{12}N_2OS$	62.09(62.07)	5.20(5.17)	12.05(12.07)
4a	3-Nitrophenyl	148	75	$C_{13}H_{11}N_3O_3S_2$	48.58(48.60)	3.45(3.43)	13.06(13.08)
4b	4-Nitrophenyl	141	71	$C_{13}H_{11}N_3O_3S_2$	48.61(48.60)	3.41(3.43)	13.10(13.08)
4c	3,4,5-Trimethoxyphenyl	117	73	$C_{16}H_{18}N_2O_4S_2$	52.49(52.46)	4.90(4.92)	7.66(7.65)
4d	3-Bromophenyl	148	70	$C_{13}H_{11}BrN_2OS_2$	43.92(43.94)	3.12(3.10)	7.93(7.89)
4e	4-Fluorophenyl	125	76	$C_{13}H_{11}FN_2OS_2$	53.09(53.06)	3.76(3.74)	9.50(9.52)
4f	3-Methoxyphenyl	123	77	$C_{14}H_{14}N_2O_2S_2$	54.93(53.90)	4.60(4.58)	9.13(9.15)
5a	3-Nitrophenyl	126	73	$C_{14}H_{13}N_3O_3S_2$	50.18 (50.15)	3.85(3.88)	12.51(12.54)
5b	4-Nitrophenyl	108	71	$C_{14}H_{13}N_3O_3S_2$	50.11 (50.15)	3.85(3.88)	12.57(12.54)
5c	3,4,5-Trimethoxyphenyl	99	70	$C_{17}H_{20}N_2O_4S_2$	53.66(53.68)	5.27(5.26)	7.33(7.37)
5d	3-Bromophenyl	75	69	$C_{14}H_{13}BrN_2OS_2$	45.56(45.53)	3.50(3.52)	*7.58(7.59)*
5e	4-Fluorophenyl	86	72	$C_{14}H_{13}FN_2OS_2$	54.57(54.55)	4.24(4.22)	*9.12(9.09)*
5f	3-Methoxyphenyl	125	75	$C_{15}H_{16}N_2O_2S_2$	56.27(56.25)	5.03(5.00)	*8.73(8.75)*
6a	3-Nitrophenyl	175	67	$C_{13}H_{10}ClN_3O_3S$	48.18 (48.22)	3.12(3.09)	*12.96(12.98)*
6b	4-Nitrophenyl	103	63	$C_{13}H_{10}ClN_3O_3S$	48.25 (48.22)	3.06(3.09)	*13.00 (12.98)*
6c	3,4,5-Trimethoxyphenyl	85	64	$C_{16}H_{17}ClN_2O_4S$	52.13(52.10)	4.60(4.61)	*7.63(7.60)*
6d	3-Bromophenyl	126	61	$C_{13}H_{10}ClBrN_2OS$	43.60(43.64)	2.83(2.80)	*7.85(7.83)*
6e	4-Fluorophenyl	182	60	$C_{13}H_{10}ClFN_2OS$	52.57(52.61)	3.39(3.37)	*9.42(9.44)*
6f	3-Methoxyphenyl	165	60	$C_{14}H_{13}ClN_2O_2S$	54.49(54.46)	4.24(4.21)	9.10(9.08)

4-thiazolidinones (4) and 2'-(substituted phenyl)-3-(5'-methyl thiazole)-5-methyl-4-thiazolidinones **(5)** and 4-(substituted phenyl)-3-chloro-1-yl-(5'-methyl thiazole)-2-azetidinones **(6)** respectively in SCHEME and TABLE 1. All the newly synthesized compounds have been assigned by elemental analysis, IR and ^{1}H NMR spectral data. The compounds are evaluated for their antibacterial and antitubercular activity.

Antibacterial activity

All the synthesized compounds were screened for their antibacterial activity by using agar diffusion method[20] against *S.aureus*, *B.subtilis*(Gram positive) and *E.coli*, *S.paratyphi-B.*(Gram negative) bacteria in nutrient agar medium. The sterilized agar media [2.4%(w/v) agar-agar, 5%(w/v) NaCl, 3%(w/v) peptone, pH (6.8 to 7.0)] was poured into petridishes and allowed to solidify. On the surface of the media microbial suspension was spread over the agar plates to solidify. A stainless steel cylinder(pre-sterilized) was used

to bore the cavities. All the synthesized compounds (100µg/ml) in DMF were placed serially in the cavities, with the help of micropipette. It is then allowed to diffuse for 10 minutes in refrigerator. The plates were incubated at 37°C for 24 hours. After incubation the diameter of zone of inhibition was measured in mm. Under similar conditions controlled experiment was carried out by using Ciprofloxacin as standard drug for comparison.

Antitubercular activity

The compounds **(3a-e)**, **(4a-e)** and **(5d)** were tested *in vitro* for their antitubercular activity against *Mycobacterium tuberculosis* $H_{37}Rv$. The antitubercular evaluation of the compounds were carried out at Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF) USA. Primary screening of the compounds for antitubercular activity have been conducted at 12.5g/ml against $H_{37}Rv$ strain in BACTEC 12B medium using the BACTEC 460 radiometric system. The data were compared with standard drug Rifampin at 0.25µg/ml concentration which showed 98% inhibition.

EXPERIMENTAL

All the melting points were determined in an open capillary and are uncorrected. The IR spectra were recorded on Perkin-Elmer 237 spectrophotometer. ^{1}H NMR spectra on a Bruker Avance DPX 300MHz spectrometer with $CDCl_3$ as a solvent and TMS as internal reference. Purity of the compound was checked on TLC using silica gel-G.

Preparation of 3-methoxy-benzylidene-5-methyl thiazole (3f)

A mixture of 3-methoxy benzaldehyde (0.01mole) and 2-amino-5-methyl thiazole (0.01mole) in benzene (50ml) was refluxed using with Dean-Stark water separator. The refluxing was continued for 4-5 hours. The excess of solvent was evaporated and the residue of Schiff base was recrystallised from ethanol to give **(3f)**. Yield 85%; m.p.105°C; IR (KBr, cm^{-1}): 1580(-C=N), 1053(C-O-C), 681(C-S-C); ^{1}H NMR($CDCl_3$): δ 2.36 (s, 3H, $-CH_3$), δ 3.76(s, 3H, $-OCH_3$), δ7.2 to 8.2(m, 4 Ar-H and 1H of thiazole), δ 8.14(s, 1H, -CH=N). Anal.Calcd. for $C_{12}H_{12}N_2OS$: C,62.07; H,5.17; N,12.07. Found: C,62.09; H,5.20; N,12.05.

Compounds**(3a-e)** were prepared similarly and their characterization data are given in TABLE 1.

Preparation of 2-(3'-methoxyphenyl)-3-(5'-methyl thiazole)-4-thiazolidinone (4f)

Thioglycolic acid (0.01mole) added to solution of Schiff base **(4f)** (0.01mole) in toluene (50ml) was refluxed for 8 hours using Dean-Stark water separator. The excess of solvent was evaporated and the residue was washed with saturated solution of $NaHCO_3$ and water, dried and product was finally recrystallised from ethanol to give (4f).

Yield 78%; m.p.123°C; IR (KBr cm^{-1}):1660 (-C=O of thiazolidinone), 1240 (C-O-C), 687(C-S-C); ^{1}H NMR ($CDCl_3$): δ 2.35(s, 3H,$-CH_3$), δ 3.70(s, 3H, $-OCH_3$), δ 4.1(dd, 2H, $-CH_2$), δ 6.61(s, 1H, –CH-Ar), δ 6.81 to 7.26(m, 4 Ar-H and 1H of thiazole). Anal. Calcd. For $C_{14}H_{14}N_2O_2S_2$: C,54.90; H,4.58; N, 9.15. Found: C,54.93; H,4.60; N, 9.13.

Compounds **(4a-e)** were prepared similarly and their characterization data are given in TABLE 1

Preparation of 2-(3'-metoxyphenyl)-3-(5'-methyl thiazole)-5-methyl 4-thiazolidinone (5f)

Thiolactic acid (0.01mole) added to solution of Schiff base **(5f)** (0.01mole) in benzene(50ml) was refluxed for 8 hours using with Dean-Stark water separator. The excess of solvent was evaporated and the residue was washed with saturated solution of $NaHCO_3$ and water, dried and product was finally recrystallised from ethanol to give **(5f)**.

Yield 76%; m.p.125°C; IR(KBr cm^{-1}): 1660(-C=O of thiazolidinone), 1233(C-O-C), 672(C-S-C); ^{1}H NMR ($CDCl_3$): δ 1.71(d, 3H, -CH-C<u>H</u>$_3$) , δ 2.35 (s, 3H, $-CH_3$), δ 3.71(s, 3H,$-OCH_3$), δ 4.25(q,1H, –C<u>H</u>-CH_3), δ 6.54(s, 1H, -CH-Ar), δ 6.80 to 7.25(m, 4 Ar-H and 1H of thiazole). Anal. Calcd. for $C_{15}H_{16}N_2O_2S_2$: C,56.25; H,5.00; N, 8.75. Found: C,56.27; H,5.03; N, 8.78.

Compounds **(6a-e)** were prepared similarly and their characterization data are given in TABLE 1

Preparation of 4-(-3'-methoxyphenyl)-3-chloro-1-yl-(5'-methyl thiazole)-2-azetidinone (6f)

Triethylamine (0.01M) was added to Schiff base

TABLE 2 : Antimicrobial activity of compounds 3a-f, 4a-f, 5a-f and 6a-f and antitubercular activity of compounds (3a-e), (4a-e), and (5d)

No.	R	Zone of inhibition (mm)				% Inhibition
		S.aureus	*B.subtilis*	*E.coli*	*S.paratyphi-B*	*M.tuberculosis* H37 Rv
3a	3-Nitrophenyl	-	11	-	-	0
3b	4-Nitrophenyl	-	12	-	-	-
3c	3,4,5-Trimethoxyphenyl	10	11	-	10	4
3d	3-Bromophenyl	14	12	-	-	-
3e	4-Fluorophenyl	13	16	-	-	0
3f	3-Methoxyphenyl	-	15	-	-	
4a	3-Nitrophenyl	11	15	-	-	65
4b	4-Nitrophenyl	-	10	12	-	54
4c	3,4,5-Trimethoxyphenyl	15	13	-	11	0
4d	3-Bromophenyl	10	11	-	12	69
4e	4-Fluorophenyl	12	-	-	-	31
4f	3-Methoxyphenyl	-	-	-	14	
5a	3-Nitrophenyl	10	13	-	10	
5b	4-Nitrophenyl	11	17	-	-	
5c	3,4,5-Trimethoxyphenyl	10	11	11	-	
5d	3-Bromophenyl	10	10	-	-	77
5e	4-Fluorophenyl	12	13	-	-	
5f	3-Methoxyphenyl	10	14	-	11	
6a	3-Nitrophenyl	10	-	12	-	
6b	4-Nitrophenyl	11	12	12	-	
6c	3,4,5-Trimethoxyphenyl	10	-	10	-	
6d	3-Bromophenyl	-	11	11	-	
6e	4-Fluorophenyl	13	13	10	-	
6f	3-Methoxyphenyl	-	16	14	-	
Standard drug	Ciprofloxacin	22	20	20	18	-

(6f) (0.01M) and chloroacteyl chloride (0.01M) in dry dioxane (30ml) at room temperature and stirred for 24 hours. The reaction mixture was kept for three days and then poured in to crushed ice. The resulting product was separated out, filtered, washed with water and recrystallised from ethanol to give **(6f)**.

Yield 60%; m.p. 165°C; IR (KBr cm^{-1}): 1737 (-C=O), 1240 (C-O-C), 742(-C-Cl); ^1H NMR ($CDCl_3$): δ 2.35 (s, 3H, $-CH_3$), δ 3.76(s, 3H,$-OCH_3$), δ 6.80 (d, 1H, -CH-Ar), δ 7.15 to 7.30(m, 4 Ar-H and 1H of thiazole), δ 8.30(d, 1H, -CH-Cl). Anal. Calcd. for $C_{14}H_{13}ClN_2O_2S$: C,54.46; H,4.21; N, 9.08. Found: C,54.49; H,4.24; N, 9.10.

Compounds **(6a-e)** were prepared similarly and their characterization data are given in TABLE 1

CONCLUSION

From the activity data, it could be observed that compound **(4c)** exhibit good activity against *S.aureus*. Compounds **(3e)**, **(3f)**, **(4a)**, **(5b)** and **(6f)** showed good activity against *B.subtilis*. All the remaining compounds were found to be less or inactive against all bacteria. All the antibacterial data are represented in TABLE 2.

Compounds **(4a)**, **(4d)** and **(5d)** showed 60-80% inhibition against Mycobacterium tuberculosis $H_{37}Rv$. The data of % inhibition are represented in TABLE 2.

It can be concluded that compound **(5d)** bearing, R=3-bromophenyl showed maximum inhibition against *Mycobacterium tuberculosis* $H_{37}Rv$.

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