RJC
http://www.rasayanjournal.com

RASĀYAN *J. Chem.*
Vol.4, No.1 (2011), 24-28
ISSN: 0974-1496
CODEN: RJCABP

SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 4-THIAZOLIDINONE CONTAINING BENZOTHIAZOLYL MOIETY

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ABSTRACT

4-Thiazolidinone has been prepared by the reaction of various substituted Schiff bases (**4a-g**) with thioglycolic acid. The intermediate schiff bases were synthesized by the condensation of substituted 2-amino benzothiazole with O-vaniline, P-vaniline, salicylialdehyde and N, N-dimethylaminobenzaldehyde. The starting compound substituted 2-aminobenzothiazole was prepared from P-toludine and phenetidine. The structure of compounds has been confirmed by elemental and spectral analysis. The antibacterial activities of the synthesized compounds have been screened against *Escherichia Coli*, *Bacillus subtilis*, *Erwinia Cartovara*, and *Xanthomonas Citri.*

Key words: Benzothiazole, Schiff-bases, 4-Thiazolidinone, Antibacterial activity.

INTRODUCTION

A survey of literature reveals that large work has been carried out on the synthesis of 4-thiazolidinone and known to exhibits various biological activities as antitubercular[1], antiallergic[2]. Schiff-bases give good antibacterial activity and pharmacological application[3]. 4-Thiazolidinone ring are reported to possess various biological activities, as antimicrobial, anti-inflammatory, antiviral, antiparasitic and antituberculosis[4-18]. These Schiff-bases can be prepared by the acid catalysed reaction of amine and aldehyde or ketone which shows good fungicidal acivity[19].

4-Thiazolidinone give good pharmacological properties[20] are known to exhibit antitubercular[21], antibacterial[22], anticonvulsant[23], antifungal activity[24]. Large work has been carried out on 4-thiazolidinone but very less information is available about 4-thiazolidinone bearing substituted benzothiazolyl moiety.

The starting compound substituted 2-hydrazino benzothizole (1) have been synthesized from substituted amine[25]. Substituted 2-hydrazino benzothiazole were condensed with various aldehyde to yield Schiff-bases (**3a-g**). The Schiff-bases were further reacted with thioglycolic acid to yield 4-thiazolidinone derivatives (**4a-g**) Scheme-1.

EXPERIMENTAL

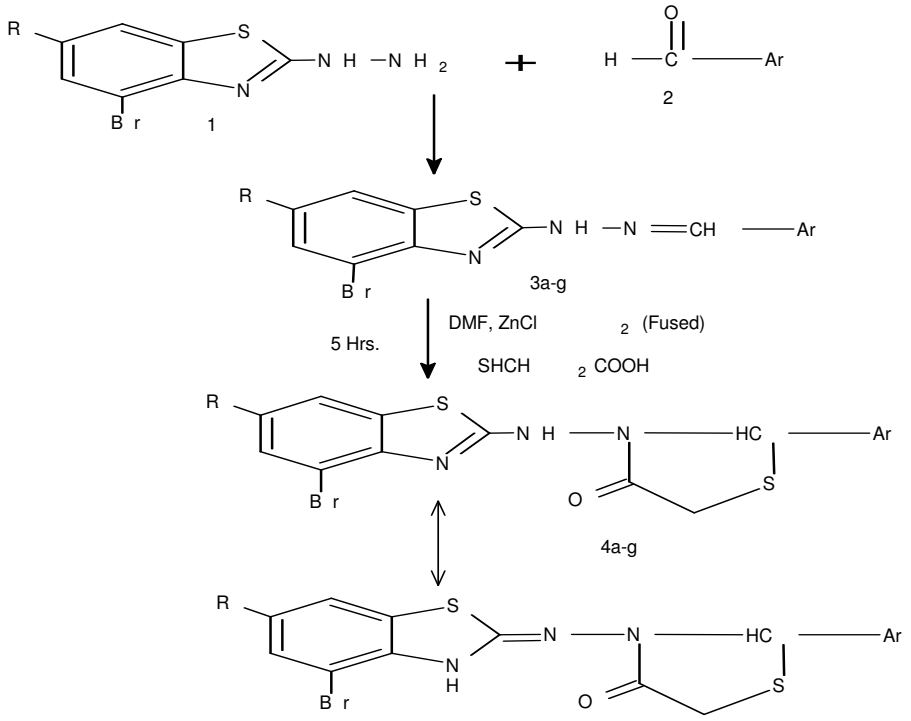
All the melting points were determined in open capillary tube and may be uncorrected. The purity of compound was checked by TLC on silica gel coated glass plate. Infra-red spectra were monitored in KBr palates on Bomen 104 FT infra-red spectrophotometer. H^1 NMR spectra were obtained on a Gemani 200 Mz spectrometer with tetra methyl silane as an internal standard. Mass spectra were recorded on FTVG-7070H mass spectrometer using the EI technique at 70ev. Elemental analysis was performed on a Heraeus CHN-O rapid analyzer.

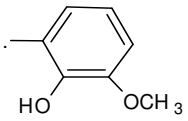
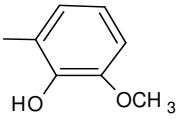
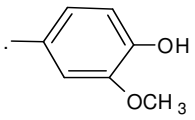
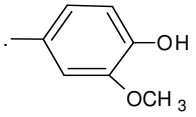
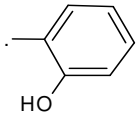
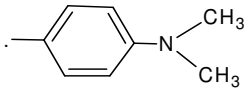
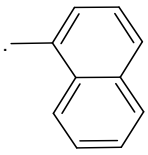
Synthesis of 4-bromo 2-substituted phenyl 6-methyl/ethoxy benzothiazolyl hydrazone (3_{a-g}):

The mixture of substituted hydrazino benzothiazole (0.01) was dissolved in ethanol (50ml) and aryl aldehyde (0.01M) was refluxed on water bath for two hours. The reaction mixture was cooled and solid obtained was filtered at pump, washed with ethanol and recrystalised from hot benzene.

3a. : Yield: 2.74 gm (70%), M. P. : 175 ^{o}C, IR(KBr) : 3160 (N-N) stretch), 1584 (C= N Stretch), 1290 (C-N Stretch), Mass (m/e) : 391 (M^{+}., 30%) and base peak at 55. [Found : C: 47.90 %, H : 10.48%, N : 3.30 %, $C_{16}H_{14}BrN_3O_2S$ required : C: 48.07%, H : 10.71%, N : 3.57 %.]
3b. : Yield : 3.05 gm (78%), M. P. : 265^{o}C. IR (KBr) : 3200 cm^{-1} (-OH Stretch), 3167 cm^{-1} (N-H Stretch), [Found : C: 48.62%; H : 10.50%; N : 3.42%, $C_{16}H_{14}BrN_3O_2S$ required : C: 48.97%; H : 10.71%; N : 3.57%
3c. : Yield : 2.6 gm (72%), M. P. : 215 ^{o}C. IR (KBr):3180 cm^{-1} (-OH Stretch), 3174 cm^{-1} (N-N Stretch). [Found : C : 49.44%; H : 3.20%; N : 11.34%, $C_{15}H_{12}BrN_3OS$ required : C : 49.72%; H : 3.31%; N : 11.60%].
3d. : Yield : 2.68 gm (68%), M. P. : 233 ^{o}C. I.R. (KBr) : 3389 (N-H stretching) 3053 (= C-H stretch in aromatic ring), 1541 (C=N stretch), 1290 (C-N stretch), [Found : C : 57.32%; H : 3.40% ; N : 10.28%, $C_{19}H_{14}BrN_3S$ required C : 57.57%; H : 3.53%; N : 10.60%]
3e. Yield : 3.0 gm (71%), M. P. 245 ^{o}C, IR (KBr):3423 cm^{-1} (O-H) stretching), 3209 cm^{-1} (N-H stretching), [Found : C : 48.12%; H : 3.62%; N : 9.58%, $C_{17}H_{16}BrN_3OS$ required : C : 48.34%; H : 3.79%; N : 9.95%]
3f. Yield : 3.2 gm (75%), M. P. : 214 ^{o}C, IR (KBr) : 3448 cm^{-1} (O-H) stretching), 3200 cm^{-1} (N-H stretching), [Found : C : 48.00%; H : 3.50%; N : 9.62%, $C_{17}H_{16}BrN_3O_3S$ required : C : 48.34%; H : 3.79%; N : 9.95%]
3g. : Yield :- 2.6 gm (62%), M. P. :- 138 ^{o}C., IR (KBr) : 3302 (N-H stretching) [Found : C : 51.32%; H : 3.62%; N : 12.96%, $C_{18}H_{19}BrN_4OS$ required C: 51.55%; H : 3.81%; N : 13.36%]

Synthesis of 2-substituted phenyl 3-substituted benzothiazolyl 4-thiazolidinone (4a-g) :
A mixture of hydrazone (Schiff-bases, **3a-g**) (0.0025M), DMF (15 ml) and thioglycolic acid (0.005) was taken in round bottom flask. Small amount of fused $ZnCl_2$ (200 mg) was added in reaction mixture. The contents of round bottom flask refluxed for five hours. Cooled and poured on crushed ice. Thus the product obtained was filtered, washed with water and recrystalised from DMF.
4a. : Yield : 0.77 gm (66%), M. P. : 158 ^{o}C, I.R. (KBr) : 3400 cm^{-1} (O-H stretching), 3163 cm^{-1} (N-H stretching), 1740 cm^{-1} (C=O) stretching); NMR : δ 2.2 (s, 2H, -CO-CH_2), δ 2.5 (s, 3H, Ar- CH_3) , δ 3.8 (s, 3H, O-CH_3), δ 6.8 (s, 1H, -OH), δ 7.0 (s, 1H, -CH), δ 7.2- 7.6 (m, 3H, Ar-H), δ 8.4 (s, 1H, N-H), δ 9.5 (s, 1H, enolic O-H), Mass : 465(M^{+}) and base peak at 244. [Found : C : 45.96%; H : 3.14%; N : 8.82%, $C_{18}H_{16}BrN_3O_3S_2$ required : C : 46.35%; H : 3.43%; N : 9.01%.]
4b. : Yield : 1.0 gm (86%), M. P. : 240 ^{o}C, I.R. (KBr) : 3400 cm^{-1} (O-H stretching), 3151 cm^{-1} (N-H stretching), 1716 cm^{-1} (C=O) stretching). [Found : C : 45.86%; H : 2.98%; N : 8.68%, $C_{18}H_{16}BrN_3O_3S_2$ required : C : 46.35%; H : 3.43%; N : 9.01%.]
4c. : Yield : 0.72 gm (67%), M. P. : 230 ^{o}C, I.R. (KBr) : 3300-3100 cm^{-1} (broad) due to –OH and N-H stretching, 1701 (C=O stretching). [Found : C : 46.23%; H : 2.94%; N : 9.04%, $C_{17}H_{14}BrN_3O_2S_2$ required : C : 46.78%; H : 3.21%; N : 9.36%.]
4d. : Yield : 0.85 gm (73%), M. P.: 94 ^{o}C, I.R. (KBr) : 3211 cm^{-1} due to N-H stretching, 1716 cm^{-1} (C=O stretching). [Found : C: 46.23%; H : 2.94%; N : 9.04%, $C_{21}H_{16}BrN_3OS_2$ required : C: 46.78%; H : 3.21%; N : 9.36%.]
4e. : Yield : 0.89 (72%), M. P. : 260 ^{o}C, I. R. (KBr) : 3400 cm^{-1} broad (O-H stretching), 3103 cm^{-1} (N-H stretching), 1716 cm^{-1} (C=O stretching). [Found : C : 45.38%; H : 3.14%; N : 8.13%, $C_{19}H_{18}BrN_3O_4S_2$ required : C : 45.96%; H : 3.62% N : 8.46%.]
4f. : Yield : 0.87 gm (70%), M. P. : 290 ^{o}C, I. R. (KBr) : 3448 cm^{-1} broad (O-H stretching), 3277 cm^{-1} (N-H stretching), 1734 cm^{-1} (C=O stretching). [Found : C : 45.52%; H : 3.41%; N : 8.19%, $C_{19}H_{18}BrN_3O_4S_2$ required : C : 45.96%; H : 3.62%; N : 8.46%.]
4g. : Yield : 0.94 (77%), M. P. : 276 ^{o}C, I. R. (KBR) : 3178 cm^{-1} (N-H stretching), 1710 cm^{-1} (C=O stretching), Mass : 493 (M^{+}. 7%). [Found : C : 48.22%; H : 3.965%; N : 11.04%, $C_{20}H_{21}BrN_4O_2S_2$ required : C : 48.68%; H : 4.25%; N : 11.35%.]



Comp.	R	Ar	Comp.	R	Ar
4a	$-CH_3$		4e	OC_2H_5	
4b	$-CH_3$		4f	OC_2H_5	
4c	$-CH_3$		4g	OC_2H_5	
4d	$-CH_3$				

Scheme-1

RESULTS AND DISCUSSION

Structures of the compounds synthesized have been confirmed by elemental analysis, IR, ^{1}HNMR and mass spectra.

I.R. Spectrum of compound (**4a**) in (KBr) shows absorption band 3163 cm^{-1} due N-H Stretching and at 1697 cm^{-1} to five membered cyclic amido C=O Stretching

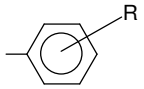
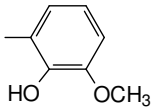
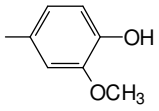
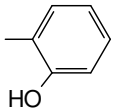
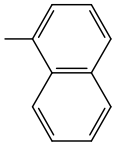
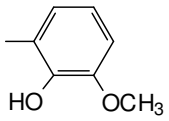
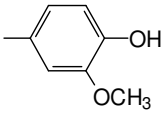
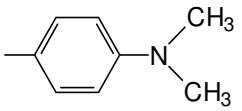
PMR Spectrum of compound (**4a**) in (dmso d_6) shows one singlet δ 2.3 due to $–COCH_2$- δ 2.5 (s) due to Ar-CH_3 δ 3.8 due to OCH_3, δ 6.7 due to –OH, δ 7.0 due to -CH-, δ 7.2-7.6 (m) due to Ar-H and δ 9.5 due to -NH. Mass spectrum of the same compound (**4a**) shows peak at 465 (M^+.) which corresponds to its molecular weight.

Similarly I.R. spectra of compounds (**4b-4g**) exhibit bands in the region 3100-3400 cm^{-1} and 1600-1800 cm^{-1} due to N-H stretching and C=O stretching respectively.
Mass spectrum of the compound (**4g**) shows mass peak at 493 (M^+) which corresponds to its molecular weight.
The PMR spectrum exhibits two singlet peaks for –NH proton (δ 8.4 and δ 9.5) which indicates that, compound (**4a**) may exists in tautomeric form.

Evaluation of antibacterial activity

The compound (**4a-g**) were tested for their antimicrobial activity by cup plate agar diffusion method against *E. Coli*, *Erwinia carotovara, Bacillus subtilis* and *Xanthomonas citri* species using ampicilin, streptomycin penicillin as a standard compound (positive control) for comparison. The antibacterial screening data of the compound are presented in Table-1.

Table-1: Antibacterial Activity of Newly Synthesized Compounds.

S. No.	Comp.		Antibacterial activity (zone of inhibition in mm)			
			E.coli	*Erwinia cartovara*	*Bacillus subtilis*	*Xanthom-onas citri*
1	4a		06	07	06	10
2	4b		14	07	08	12
3	4c		13	10	09	14
4	4d		12	10	08	07
5	4e		10	06	06	08
6	4f		08	06	00	06
7	4g		08	06	08	08
Ampicillin			16	18	17	15
Streptomycin			20	18	22	18
Penicillin			15	20	18	17
Control			00	00	00	00

CONCLUSION

From the results it is clear that the compounds tested showed variable toxicity against different bacteria. This variation in toxicity can be attributed to different structures and functional groups attached to the basic nucleus. It is also clear from the results presented in table-2 that phenolic –OH and aryl substituted $–OCH_3$ groups in the basic nucleus, the antibacterial activity was increased. This was observed with bacteria that the subsequent addition of phenolic (-OH) and aryl substituted $–OCH_3$ groups antibacterial activity was enhanced.

ACKNOWLEDGEMENTS

The authors are grateful to principal, Science College, Nanded for providing laboratory facilities, Director, Indian Institute of Chemical Technology, Hydrabad for providing spectra and Dr. V. N. Kadam, Principal, G. S. Gawande College, Umarkhed, for encouragement.

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[RJC-698/2010]