Synthesis and Antibacterial Activity of Schiff bases and 4-Thiazolidinones

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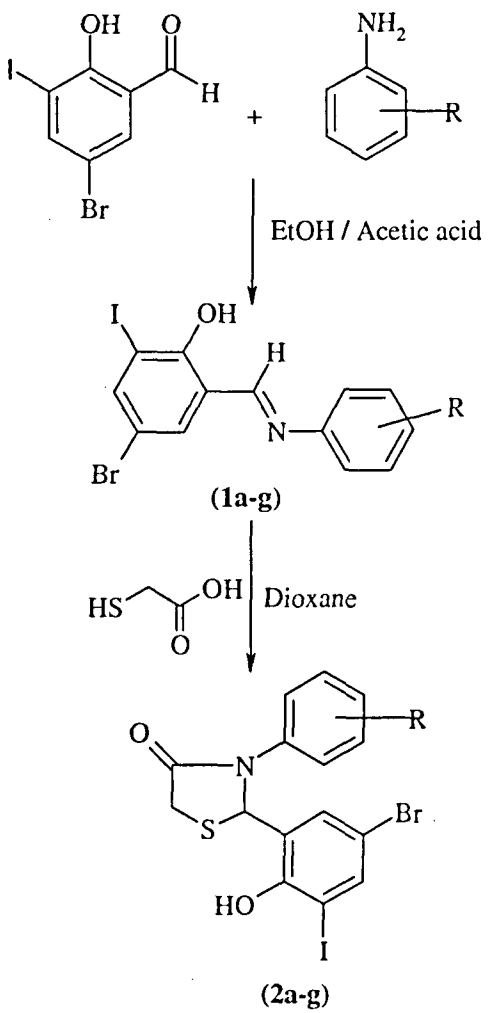
Some new Schiff bases (1a-g), 4-thiazolidinones (2a-g) have been synthesized and tested for their antibacterial activity. The structures of these compounds have been established on the basis of elemental analysis and spectral data (IR and ^{1}H NMR).

Schiff bases and 4-thiazolidinones have been claimed to possess higher degree of anticancer and antitubercular activity[1,2], the biological activity of schiff bases were due to >C=N linkage and the activity of 4-thiazolidinones were due to -C-N-S linkage. The schiff bases were synthesized by the condensation of 2-hydroxy naphthaldehyde with different amine[3], the Schiff bases possess antitubercular[4], antitumour[5], fungicidal[6], medicinal and agrochemical[7] activity. 4-Thiazolidinones have attracted considerable attention as they were also endowed with wide range of pharmaceutical activities. 4-Thiazolidinones from hydrazide, aromatic aldehydes and thioglycolic acid were found to be analgesic, antiseptic[8]. 4-Oxathiazolidinones and 2-amino 4-oxathiazolidinones were reported as anti HIV, anticancer and antitubercular agents[9]. Various 4-thiazolidinones derivatives occupy an important place in medicinal chemistry as they show a variety of pharmacological and microbiological activities[10-13], therefore an attempt was made to study the antibacterial activity of some new schiff bases and 4-thiazolidinones prepared in the present investigation.

Schiff bases (**1a-g**) were synthesized by the condensation of 2-hydroxy-3-iodo-5-bromobenzaldehyde with aromatic amine in ethanol. Compounds (**1a-g**) on cyclisation with mercapto acetic acid afforded corresponding 4-thiazolidinones (**2a-g**) as shown in Scheme 1. Melting points were uncorrected. IR spectra were recorded in nujol on Perkin-Elmer-237 spectrophotometer. ^{1}H NMR were recorded in $CDCl_3$ on a Perkin-Elmer-R-32 spectrometer using TMS as internal standard (chemical shift are given in δ ppm).



Scheme 1: Synthetic scheme of Schiff bases prepared in this investigation.

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TABLE 1: ANALYTICAL AND ACTIVITY DATA OF COMPOUNDS 1a-g AND 2a-g.

Entry	R	Molecular formula	m. p. (°)	Yield (%)	Zone of inhibition in mm*			
					E. c	*B. s*	*S. t*	*S. d*
1a	H	$C_{13}H_9NOBrI$	120	71	05	06	07	08
1b	2-OCH_3	$C_{14}H_{11}NO_2BrI$	115	64	18	17	19	18
1c	4-Cl	$C_{13}H_8NOBrClI$	114	68	19	18	17	18
1d	4-CH_3	$C_{14}H_{11}NOBrI$	145	65	17	15	19	18
1e	2-COOH	$C_{14}H_9NO_3BrI$	92	61	05	07	04	03
1f	2-NO_2	$C_{13}H_8N_2O3BrI$	140	66	06	05	07	06
1g	4-NO_2	$C_{13}H_8N_2O_3BrI$	145	85	05	06	07	04
2a	H	$C_{15}H_{11}NO_2SBrI$	210	65	08	06	04	07
2b	2-OCH_3	$C_{16}H_{12}NO_3SBrI$	240	55	18	17	19	16
2c	4-Cl	$C_{15}H_{10}NO_2SBrClI$	190	83	18	16	17	19
2d	4-CH_3	$C_{16}H_{13}NO_2SBrI$	141	68	17	16	18	17
2e	2-COOH	$C_{16}H_{11}NO_4SBrI$	210	79	03	04	07	08
2f	2-NO_2	$C_{15}H_{10}N2O_4SBrI$	147	70	07	05	04	08
2g	4-NO_2	$C_{15}H_{10}N2O_4SBrI$	189	82	06	07	08	03
Tetracycline					20	20	20	20

*Diameter of disc is 5 mm. *E. c-Escherischia coli. B. s- Bacillus subtilis, S. t- Salmonella typhi* and *S. d- Salmonella dysentrae.*

To a mixture of 2-hydroxy-3-iodo-5-bromobenzaldehyde (10 mmol) and p-toludiene (10 mmol) dissolved in ethanol, one drop of acetic acid was added. The reaction mixture was refluxed for 2 h. The content were poured on ice cooled water, separated solid was dried and crystallized from ethanol. IR (ν_{max}): 1635 (C=N), 1580, 1442 (C=C). ^{1}H NMR ($CDCl_3$): 2.2 (s, 3H, CH_3), 8.5 (s, 1H, CH=N), 13.1 (s, 1H, OH), 7.0-7.5 (m, 6H, Ar-H). Anal. Cald. For $C_{14}H_{11}NOBrI$ (416.06): C, 40.42; H, 2.66; N, 3.37; Found C, 40.37; H, 2.63, N, 3.35.

To a solution of compound 1d (10 mmol) in dry diaxone (10 ml), a solution of mercapto acetic acid (10 mmol) in dry diaxone (10 ml) was added followed by catalytic amount of $ZnCl_2$ (15 mg) and the reaction mixture was refluxed for 8 h. The reaction was monitored by TLC. Solvent was evaporated under reduced pressure and separated residue was neutralized by sodium bicarbonate to remove excess of mercapto acetic acid. Solid compound obtained was crystallized from ethanol. IR (ν_{max}): 1665 (C=O), 1585, 1470 (C=C). ^{1}H NMR ($CDCl_3$): 2.3 (s, 3H, CH_3), 4.2 (s, 2H, CH2), 6.9 (s, 1H, N-CH), 7.5-8.5 (m, 6H, Ar-H), 13.3 (s, 1H, OH). Anal. Cald. For $C_{16}H_{13}NO_2SbrI$ (490.16): C, 39.21; H, 2.67; N, 2.86; Found: C, 39.18; H, 2.66; N, 2.81.

Antibacterial activity was determined using disc diffusion method[14] by measuring zone of inhibition. All the compounds were screened for their antibacterial activity using *Escherischia coli, Bacillus subtilis, Salmonella typhi* and *Salmonella dysentraeas as* test organisms. The compounds were tested at 150 ppm concentration using 5 mm filter paper disc. Control experiment was carried out under similar condition by using tetracycline as a standard for comparison. The inhibition zone measured in mm showed that compounds 1b, 1c, 1d, 2b, 2c and 2d were more active than other compounds tested against the above microbes, but none showed better or comparable activity to tetracycline (Table 1).

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REFERENCES

1. Pawar, R.P., Andurkar, N.M. and Vibhute, Y.B., **J. Indian Chem. Soc.**, 1999, **76**, 271.
2. Pawar, R.P., Andurkar, N.M., Patil, B.R. and Vibhute, Y.B., **Hindustan Antibiot. Bull.**, 1998, **40**, 51.
3. Nadir, U.K and Chaurasia, B.P., **Indian J. Chem.**, 1992, **31B**,189.
4. Marchant, J.R. and Chothia, D.S., **J. Med. Chem.**, 1970, **13**, 335.
5. Deliwala, C.V., Sabnis, S.S. and Modi, J.D., **J. Med. Chem.**, 1971, 14, 450.
6. Panditrao, P.R., Deval, S.D., Gupta, S.M., Samant, S.D. and Deodhar, L.D., **Indian J. Chem.**, 1981, **20B**, 929.
7. Dincer, S., **Indian J. Chem.**, 1996, **33B**, 1335.
8. Astik, R.R., Achary, J.N., Joshi, G.B. and Thaker, K.D., **J. Indian Chem. Soc.**, 1976, **53**, 272.
9. Bhatt, J.J., Shah, B.R., Trivedi, P.B., Uhadavia, N.K. and Desai, N.C., **J. Indian Chem. Soc.**, 1994, **33B**, 189.
10. Joshi, N., Patel, P. and Parekh, H., **Indian J. Chem.**,1996. **35B**, 867.
11. Parmar, J.M., Modha, J.J. and Parekh, A.R., **Indian J. Chem.**, 1999, **38B**, 440.
12. Andres, C.J., Bronson, J.J., Andrea, S.V. D., Deshpande, M.S., Falke, P.J., Grantyoung, K.A., Harte, W.E., Ho, H.T., Misco, P.F., Robertson, J.J., Yaxiongsan D.S., and Walsh A.W., **Bioorg. Med. Chem. Lett.**, 2000, 10, 715.
13. Barreca, M.L., Chimirri, A., Luca, L.D., Monfort, A.M., Rao, A., Zappla, M., Balzarini, G., Clercq, E.D., Pannecouque, C. and Witvrolav, M., **Bioorg. Med. Chem. Lett.**, 2001, 11, 1793.
14. Collins, C.H., Microbiological Methods, London, 1974.

Reverse Phase HPLC Method for Simultaneous Estimation of Tizanidine Hydrochloride and Nimesulide in Tablets

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A reverse phase high performance liquid chromatography method for the simultaneous estimation of tizanidine hydrochloride and nimesulide in tablets is presented. Cynopropyl column is used to retain tizanidine hydrochloride (k'=1.52) and also have reasonable retention for nimesulide (k'=2.37) with a good resolution and peak symmetry. Effect of change of chromatographic conditions such as pH, %organic modifier (acetonitrile) in mobile phase on retention of drugs were studied and optimized. Both the drugs showed linear response in the concentration range employed (tizanidine hydrochloride, 1.2-2.8 μg/ml and nimesulide, 60-140 μg/ml) and was validated by least squares method at 95% confidence level. The results of analysis have been validated statistically and by recovery studies. The mean recoveries obtained for tizanidine hydrochloride and nimesulide were 99.6% and 100.1%, respectively.

Nimesulide (NIM), 4'-Nitro-2'-phenoxymethanesulphonanilide, is widely used as an analgesic, antiinflammatory and antipyretic drug[1]. It acts as an inhibitor of prostaglandin synthetase and platelet aggregation. Tizanidine hydrochloride (TIZ), 5-chloro-N-(4,5-dihydro-1H-imidazole-2-yl)-2,1,3 benzothiadiazole, is a centrally acting muscle relaxant[2]. A combination of both these drugs, NIM (100 mg) and TIZ (2 mg) in each tablet, is marketed by Unichem Laboratories (Zulu).

Both these drugs are not official with United States Pharmacopoeia, Edn. 24 or European Pharmacopoeia 2000. A literature survey revealed no reported analytical methods for the simultaneous determination of TIZ and NIM either as

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