

Synthesis and Antimicrobial Activity of Some New Schiff Bases, 4-Thiazolidinones and 2-Azetidinones

S.R. BHUSARE, S.S. ARDHAPURE, W. N. JADHAV, R. P. PAWAR*
and Y. B. VIBHUTE†

Organic Chemistry Synthesis Laboratory, Dnyanopasak College, Parbhani-431 401, India.
E-mail: bhusare71@yahoo.com Fax: 91-02452-20618

Some new heterocyclic Schiff bases **1** were synthesized from 2-amino- α -naphthothiazole. Further these heterocyclic Schiff bases were converted into 4-thiazolidinones **2** and 2-azetidinones **3** by the action of mercaptoacetic acid and chloroacetyl chloride respectively. Structure elucidation of compounds **1**, **2** and **3** has been made on the basis of elemental analysis, IR and ^1H NMR data. The biological screening data of **1**, **2** and **3** are also presented.

Key words: Synthesis, Schiff Bases, 4-thiazolidinones, 2-azetidinones

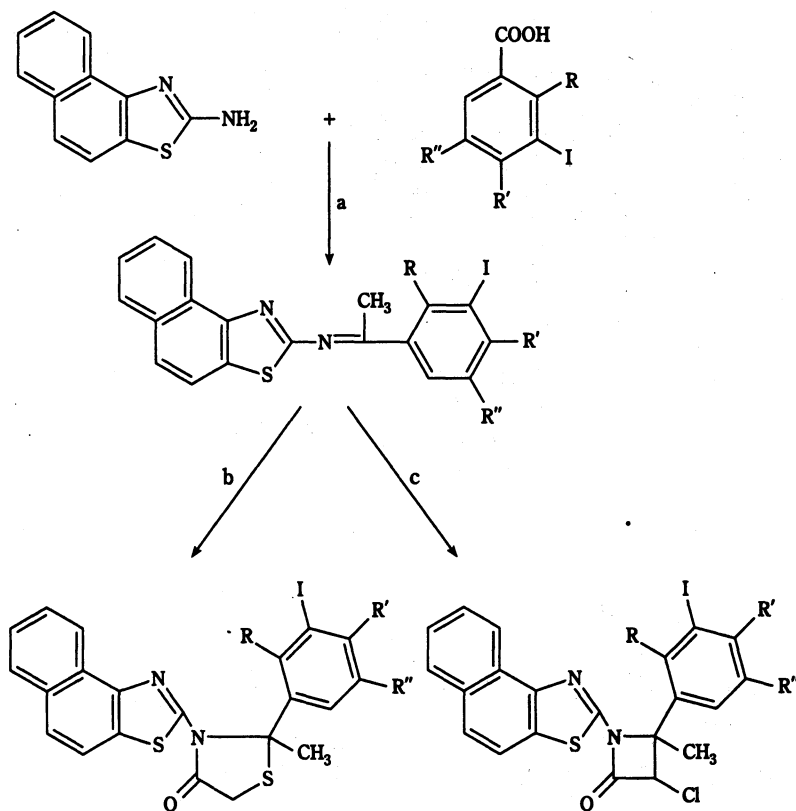
INTRODUCTION

Heterocyclic compounds of Schiff bases like 4-thiazolidinones and 2-azetidinones are reported as anticancer compounds¹⁻³. Benzothiazole derivatives are well known biologically active compounds⁴⁻⁷. Schiff bases from benzaldehyde and 1-aminophenyl thiazole are reported to have significant anticancer activity.⁸ Among the Schiff bases without alkylating nitrogen mustard moiety has been found to be highly active against *Ehrlichascites carcinoma*, *Sarcoma-180* and *Yoshida sarcoma*. It has been suggested that the azomethine linkage might be the structural requirement for the activity. Further, the biological activity of certain organic compounds has been related to their ability for complex formation with metal ions. 4-Thiazolidinones were known for their versatile pharmacological and industrial importance, though the 4-thiazolidinones containing heterocyclic moieties have been reported recently⁹⁻¹². All 2-azetidinones contain the β -lactam moiety¹³⁻¹⁵. Its reactivity is greatly influenced by substituents or fused rings¹⁶. 2-Azetidinones and their derivatives possess a variety of therapeutic activities¹⁷. All these observations and the essential role of heterocyclic Schiff bases, 4-thiazolidinones and 2-azetidinones, in certain biological reactions prompted us to synthesize **1**, **2** and **3**.

Substituted iodoacetophenones on condensation with various substituted 2-amino α -naphthothiazole furnished the Schiff bases **1** (**a-d**). These Schiff bases on cyclo condensation with mercapto-acetic acid in dioxane and in presence of

anhydrous zinc chloride afforded 4-thiazolidinones **2** (a-d). Schiff base **1** on reaction with chloroacetyl chloride in dioxane and in presence of triethylamine yields 2-azetidiones **3** (a-d) (Scheme-1). Further, the structures of compounds were deduced on the basis of elemental analysis and spectral data (IR and ^1H NMR).

SCHEME-1



The compounds synthesized were screened for their antibacterial activity using *Escherichia coli* (EC), *Salmonella typhi* (ST) and *Salmonella dysenteriae* (SD) bacteria. The activities of these compounds were tested using disc diffusion method¹⁸ at 150 ppm concentration using 5 mm filter paper disc. Tetracycline, an antibiotic, was used as a standard for comparison. The area of inhibition was measured. Compounds **1d**, **2a**, **2d**, **3a**, and **3d** showed good antibacterial activity. The remaining compounds showed moderate to less activity.

EXPERIMENTAL

All m.p.s were determined in open capillaries in a liquid paraffin bath and are uncorrected. Purity of compounds was checked by TLC. IR spectra were recorded in nujol on Perkin-Elmer-237 spectrophotometer. ^1H NMR were recorded in CDCl_3 on a Perkin-Elmer R-32 spectrometer using TMS as internal standard (Chemical shifts are given in δ ppm).

Preparation of 2-N-(2-hydroxy-3,5-diiodo- α -methyl benzylidene)- α -naphthothiazole (1a-d)

A mixture of 2-hydroxy, 3,5-diiodoacetophenone (0.001 mol) and 2-amino- α -naphthothiazole (0.001 mol) were dissolved in ethyl alcohol (25 mL). One drop of acetic acid was added to it and was refluxed for 2 h. The resultant solution was cooled and poured in cold water. The separated solid was filtered, crystallized from ethyl alcohol to give **1a**. ν_{\max} 1630 (C=N) and 1600, 1590 cm^{-1} (C=C). $^1\text{H NMR}$: δ 2.5 (s, 3H, CH_3), 6.8–8.4 (m, 8H, Ar-H) and 8.8 (s, 1H, Ar-OH). Similarly other compounds were also prepared (Table-1).

TABLE-1
PHYSICAL AND ANTIBACTERIAL DATA OF COMPOUNDS
1 (a-d), 2 (a-d) AND 3 (a-d)

S.No.	R	R'	R''	m.f.	m.p. ($^{\circ}\text{C}$)	Yield (%)	Zone of inhibition in mm		
							EC	SD	ST
1a	OH	H	I	$\text{C}_{19}\text{H}_{12}\text{N}_2\text{OSI}_2$	86	75	08	04	05
1b	H	OH	I	$\text{C}_{19}\text{H}_{12}\text{N}_2\text{OSI}_2$	125	70	04	06	02
1c	OH	H	Cl	$\text{C}_{19}\text{H}_{12}\text{N}_2\text{OSCl}$	58	65	06	04	08
1d	OH	H	Br	$\text{C}_{19}\text{H}_{12}\text{N}_2\text{OSBr}$	135	68	17	18	16
2a	OH	H	I	$\text{C}_{21}\text{H}_{14}\text{N}_2\text{O}_2\text{S}_2\text{I}_2$	165	72	18	16	17
2b	H	OH	I	$\text{C}_{21}\text{H}_{14}\text{N}_2\text{O}_2\text{S}_2\text{I}_2$	280	65	04	05	08
2c	OH	H	Cl	$\text{C}_{21}\text{H}_{14}\text{N}_2\text{O}_2\text{S}_2\text{Cl}$	82	69	07	05	03
2d	OH	H	Br	$\text{C}_{21}\text{H}_{14}\text{N}_2\text{O}_2\text{S}_2\text{Br}$	210	73	17	13	14
3a	OH	H	I	$\text{C}_{21}\text{H}_{13}\text{N}_2\text{O}_2\text{SClI}_2$	140	63	18	16	14
3b	H	OH	I	$\text{C}_{21}\text{H}_{13}\text{N}_2\text{O}_2\text{SClI}_2$	66	68	07	05	06
3c	OH	H	Cl	$\text{C}_{21}\text{H}_{13}\text{N}_2\text{O}_2\text{SCl}_2\text{I}$	108	70	03	06	04
3d	OH	H	Br	$\text{C}_{21}\text{H}_{13}\text{N}_2\text{O}_2\text{SBrClI}$	72	74	18	16	14

Preparation of 2-methyl-2-(2-hydroxy, 3,5-diiodophenyl)-3-(α -naphthothiazolyl)-4-thiazolidinone (2a-d)

A mixture of compound **1a** (0.001 mol) and mercaptoacetic acid (0.001 mol) were dissolved in dioxane (20 mL). A pinch of anhydrous zinc chloride was added and then refluxed for 8 h. The separated solid was filtered, washed with sodium bicarbonate solution and then recrystallised from ethyl alcohol to give **2a**. ν_{\max} 1670 (C=O) and 1630–1560 cm^{-1} (C=C). $^1\text{H NMR}$: δ 1.9 (s, 3H, CH_3), 2.35 (s, 2H, CH_2S), 6.9–8.2 (m, 8H, Ar-H) and 8.5 (s, 1H, Ar-OH). Similarly other compounds were also prepared (Table-1).

Preparation of 1-(α -naphthothiazolyl)-3-chloro-4-(2-hydroxy-3,5-diiodophenyl)-2-azetidinone (3a-d)

A mixture of compound 1a (0.001 mol) and triethylamine (0.003 mol) were dissolved in dioxane (25 mL). Chloroacetyl chloride (0.0012 mol) was added dropwise at 10°C. The reaction mixture was stirred for 6 h. Half of the solvent was removed by distillation and then cooled. The solid separated out was crystallized from chloroform to give 3a. ν_{\max} 1760 ν (C=O) and 1600 cm^{-1} (C=C). $^1\text{H NMR}$: δ 1.8 (s, 3H, CH_3), 4.6 (s, 1H; CH-Cl), 7.2–8.2 (m, 8H, Ar—H) and 8.7 (s, 1H, Ar—OH). Similarly other compounds were also prepared (Table-1).

All compounds gave satisfactory C, H, and N analysis.

ACKNOWLEDGEMENT

The authors are thankful to Dr. B.M. Bhawal, Dr. P.P. Wadgaonkar and Dr. U.R. Kalkote, National Chemical Laboratory, Pune for valuable guidance.

REFERENCES

1. R.P. Pawar, N.M. Andurkar and Y.B. Vibhute, *J. Indian Chem. Soc.*, **76**, 271 (1999).
2. R.P. Pawar, N.M. Andurkar, B.R. Patil and Y.B. Vibhute, *Hind. Antibiot. Bull.*, **40**, 51 (1998).
3. R.P. Pawar, N.M. Andurkar, S.R. Bhusare and Y.B. Vibhute, *Orient. J. Chem.*, **15**, 157 (1999).
4. L. Farkas, *Ber. Offen.*, 2,453,147 (Cl. CO7D), 9th Oct. 1975; *Chem. Abstr.*, **84**, 31047 (1976).
5. R. J. Alaimo, US Pat. 4,012,409 (Cl. 260–305, CO7D) 419/001, 15th Mar. 1977; *Chem. Abstr.*, **87**, 5952 (1977).
6. N. Saldabols, J. Popelis, A. Zile and L. Kruzmetru, *Khim. Farm. Zh.*, **8**, 25 (1974).
7. M. Patra, S.K. Mahapatra and B. Dash, *J. Indian Chem. Soc.*, **51**, 1031 (1974).
8. D. Modi, S.S. Sabnis and C.V. Deliwala, *J. Med. Chem.*, **13**, 935 (1970).
9. K.H.M. Hassan and A.A. Abdelwahab, *J. Indian Chem. Soc.*, **56**, 290 (1979).
10. R.C. Gupta, K.P. Bhargav and K. Kishor, *J. Indian Chem. Soc.*, **55**, 832 (1978).
11. Raj Singh, *J. Indian Chem. Soc.*, **53**, 595 (1976).
12. K.P. Jadhav and D.B. Ingle, *J. Indian Chem. Soc.*, **55**, 424 (1978).
13. T. Kamiya, M. Hashimoto, O. Nakaguchi and T. Oka, *Tetrahedron*, **35**, 323 (1979).
14. H. Gilmann and M. Speeter, *J. Am. Chem. Soc.*, **65**, 2255 (1943).
15. D.B. Boyd, *J. Med. Chem.*, **26**, 1010 (1983).
16. G. Maffi, *Chem. Abstr.*, **53**, 8433 (1959).
17. A.K. Bose, M.S. Mannan, J.C. Kapir and S.P. Sharma, *J. Med. Chem.*, **17**, 541 (1974).
18. C.H. Collins, *Microbiological Method*, Butterworths, London, p. 364 (1974).