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SYNTHESIS OF SOME NEW HETEROCYCLIC SCHIFF BASES, 4–THIAZOLIDINONES AND 2–AZETIDINONES AS AN ANTIBACTERIAL AND ANTIFUNGAL AGENT

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ABSTRACT

Some new heterocyclic Schiff bases (**1a–h**) were synthesized from 2–amino–6–substituted benzothiazoles. Further these heterocyclic Schiff bases were converted into 4–thiazolidinones (**2a–h**) and 2–azetidinones (**3a–h**) by the action of mercaptoacetic acid and chloroacetyl chloride respectively. The biological screening data of the synthesized compounds were also presented.

Key words : Schiff bases, 4–Thiazolidinone, 2–Azetidinone, Antibacterial, Antifungal.

INTRODUCTION

Heterocyclic compounds of Schiff bases like 4–thiazolidinones and 2–azetidinones are reported as anticancer[1–3]. Schiff bases possess diversified biological applications[4,5]. Various 4–thiazolidinones show a variety of pharmacological activities[6,7]. Moreover, compounds containing 2–azetidinone ring system are shown to possess marked biological activities[8–11]. Various 4–thiazolidinones inhibit the bacterial enzyme in biosynthesis of polymers[12]. All these observations and the essential role of heterocyclic compounds prompted us to synthesize Schiff bases (**1a–h**), 4–thiazolidinones (**2a–h**) and 2–azetiditinones (**3a–h**).

2–hydroxy–3–iodo–5–bromo/chloro benzaldehyde on condensation with 2–amino–6–substituted benzothiazole furnished the Schiff bases (**1a–h**). These Schiff bases on cyclo condensation with mercapto acetic acid in dioxane and in presence of anhydrous zinc chloride afforded 4–thiazolidinones (**2a–h**). Schiff bases (**1a–h**) on reaction with chloroacetyl chloride in dioxane and in presence of triethylamine yield 2–azetidinones (**3a–h**) (Scheme 1). Further the structure of compounds were deduced on the basis of elemental analysis and spectral data (IR and ^{1}H NMR).

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Antimicrobial Activity

The compounds synthesized were screened for their antibacterial activity using *Escherischia coli* (EC). *Salmonella typhi (ST) and Salmonella dysentrae (SD)* as bacteria. The activities of these compounds were tested using disc diffusion method[13] at 150 ppm. concentration using 5 mm filter paper disc. Tetracycline an antibiotic was used as a standard for comparison. The area of inhibition of zone was measured. Compounds **1a, 1d, 1h, 2a, 2g, 3a** and **3d** showed good antibacterial activity. Remaining other compounds showed moderate to less activity.

The antifungal activity was tested against the fungal species *Aspergillus niger* (AN), *Penicillium notatum* (PN) and *Alternaria tenuissiama* (AT) at 150 ppm concentration. The antifungal data revealed the compounds **1d, 1e, 2d, 2h, 3b** and **3h** to be moderately active against the fungi. Other compounds were found to be less active against the same fungal species.

EXPERIMENTAL

Melting points 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. ^{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).

Preparation of 2–N–(2–hydroxy–3–iodo–5–bromo benzylidene)–6–methoxy benzothiazole (1e)

A mixture of 2–hydroxy–3–iodo–5–bromo benzaldehyde (0.001 mole) and 2–amino–6–methoxy benzothiazole (0.001 mole) were dissolved in ethyl alcohol (25 mL). One drop of acetic acid was added and was refluxed for 2 hrs. The resultant solution was cooled and poured in cold water. The separated solid was filtered, crystallized from ethyl alcohol to give **1e**. ν_{max} 1630 (C=N) and 1590 cm^{-1} (C=C). ^{1}H NMR: δ 4.2 (s, 3H, OCH_3), 6.9–7.4 (m, 5H, Ar–H), 6.7 (s, 1H, CH=) and 7.5 (s, 1H, Ar–OH). Similarly other compounds were also prepared (Table 1).

Preparation of 2–(2–hydroxy–3–iodo–5–bromo phenyl)–3–(6–methoxybenzothiazoly)–4–thiazolidinone (2e)

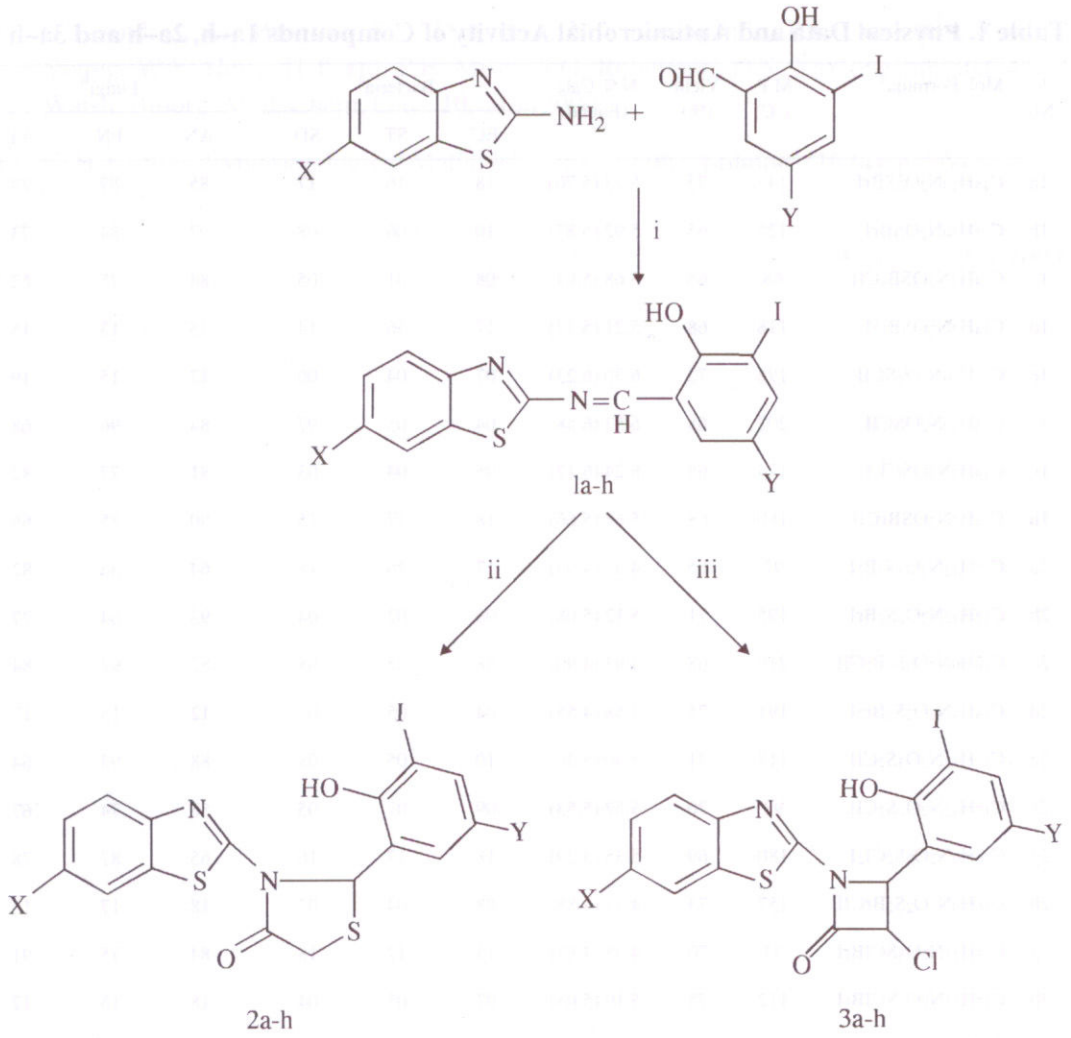
A mixture of compound **1e** (0.001 mole) and mercapto acetic acid (0.001 mole) were dissolved in dioxane (20 mL). Pinch of anhydrous zinc chloride was added and then refluxed for 8 hrs. Separated solid was filtered, washed with sodium bicarbonate solution and then crystallized from ethyl alcohol to give **2e.** ν_{max} 1665 (C=O) and 1580–1630 cm^{-1} (C=C).

^{1} H NMR: δ 3.9 (s, 3H, OCH_3), 4.5 (s, 2H, CH_2S), 6.5 (s, 1 H, N–CH), 7.0–7.9 (m, 5H, Ar–H) and 8.9 (s, 1H, Ar–OH). Similarly other compounds were also prepared (Table 1).

Table 1. Physical Data and Antimicrobial Activity of Compounds 1a–h, 2a–h and 3a–h

S. No.	Mol. Formula	M.P. (°C)	Yield (%)	N % Calc. (Found)	Bacteria[a]			Fungi[b]		
					EC	ST	SD	AN	PN	AT
1a	$C_{15}H_{10}N_2O_2SBrI$	147	73	5.73 (5.70)	18	16	17	85	87	78
1b	$C_{15}H_{10}N_2OSBrI$	125	65	5.92 (5.87)	10	06	08	97	84	73
1c	$C_{14}H_7N_2OSBrClI$	68	65	5.68 (5.64)	08	01	05	84	75	82
1d	$C_{14}H_7N_2OSBr_2I$	118	68	5.21 (5.17)	17	16	14	15	13	15
1e	$C_{15}H_{10}N_2O_2SClI$	198	72	6.30 (6.23)	07	04	06	17	15	19
1f	$C_{15}H_{10}N_2OSClI$	202	68	6.53 (6.48)	04	05	07	84	96	68
1g	$C_{14}H_7N_2OSCl_2I$	174	65	6.24 (6.17)	05	04	03	81	77	82
1h	$C_{14}H_7N_2OSBrClI$	180	68	5.68 (5.66)	18	17	15	90	85	66
2a	$C_{17}H_{12}N_2O_3S_2BrI$	92	65	4.97 (4.93)	17	16	18	64	56	82
2b	$C_{17}H_{12}N_2O_2S_2BrI$	195	71	5.12 (5.08)	06	02	04	93	64	77
2c	$C_{16}H_9N_2O_2S_2BrClI$	210	68	4.93 (4.90)	08	05	08	82	97	84
2d	$C_{16}H_9N_2O_2S_2Br_2I$	191	75	4.58 (4.55)	04	05	07	12	15	17
2e	$C_{17}H_{12}N_2O_3S_2ClI$	118	71	5.40 (5.36)	10	05	08	88	93	64
2f	$C_{17}H_{12}N_2O_2S_2ClI$	93	70	5.57 (5.53)	09	07	05	56	74	67
2g	$C_{16}H_9N_2O_2S_2Cl_2I$	180	69	5.35 (5.29)	18	17	16	65	87	78
2h	$C_{16}H_9N_2O_2S_2BrClI$	157	73	4.93 (4.88)	08	04	07	18	17	16
3a	$C_{17}H_{11}N_2O_3SClBrI$	93	70	4.95 (4.87)	15	17	18	84	75	91
3b	$C_{17}H_{11}N_2O_2SClBrI$	112	75	5.10 (5.03)	07	05	04	18	15	17
3c	$C_{16}H_8N_2O_2SCl_2BrI$	108	65	4.91 (4.86)	04	03	01	48	87	64
3d	$C_{16}H_8N_2O_2SClBr_2I$	119	73	4.56 (4.49)	19	17	18	85	47	63
3e	$C_{17}H_{11}N_2O_3SCl_2I$	110	73	5.38 (5.27)	05	04	03	84	76	85
3f	$C_{17}H_{11}N_2O_2SCl_2I$	75	68	5.55 (5.48)	07	05	04	76	64	53
3g	$C_{16}H_8N_2O_2SCl_2I$	120	67	5.33 (5.29)	08	04	06	58	47	33
3h	$C_{16}H_8N_2O_2SCl_2BrI$	109	65	4.91 (4.87)	10	08	04	18	17	15
				Tetracycline	20	21	20	–	–	–
				Greseofulvin	–	–	–	15	20	15

[a] Zone of inhibition in mm, [b] % of germination after 12 hr.



2a-h 3a-h

1,2 & 3a,e X = OCH_3 1,2 & 3a-d, Y = Br

b,f X = CH_3 1,2 & 3e-h, Y = Cl

c,g X = Cl

d,h X = Br

Reagents (i) EtOH (ii) HS – CH_2 – COOH, $ZnCl_2$/Dioxane (iii) Cl – CH_2 – COCl, Et_3N/Dioxane

Scheme - 1

Preparation of 1–(6–methoxybenzothiazolyl)–3–chloro–4–(2–hydroxy–3–iodo–5–bromo phenyl)–2–azetidinone (3e)

A mixture of compound **1e** (0.001 mole) and triethylamine (0.003 mole) were dissolved in dioxane (25 mL). Chloroacetyl chloride (0.0012 mole) was added dropwise at 10°C. The reaction mixture was stirred for 6 hrs. Half of the solvent was removed by distillation and then cooled. Separated out solid was crystallized from chloroform to give **3e**. ν_{max} 1780 (C=O) and 1666, 1599 cm^{-1} (C=C). 1H NMR: δ 3.8 (s, 3H, OCH_3), 4.2 (d, 1H, N–CH), 4.6 (d, 1H, CH–Cl), 6.7–7.7 (m, 5H, Ar–H) and 9.2 (s, 1H, Ar–OH). Similarly other compounds were also prepared (Table 1).

All compounds gave satisfactory C, H and N analysis.

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