

Research Article

**SYNTHESIS AND ANTIMICROBIAL ACTIVITY EVALUATION OF
SOME SCHIFF BASES DERIVED FROM 2-AMINOTHIAZOLE
DERIVATIVES**

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ABSTRACT

Various substituted acetophenones (1-5) on treatment with iodine and thiourea yielded 2-amino-4-(substituted-phenyl)-thiazole (1a-5a), which on further treatment with various substituted aldehydes to get N-(substitutedbenzylidene)-4-(substitutedphenyl)thiazol-2-amine (1b-5b). All the synthesized compounds were characterized by their respective FTIR, ¹H NMR and Mass data. Synthesized compounds (1b-5b) were subjected to investigation for their antibacterial and antifungal studies against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, *Asperigillus flavus* and *Asperigillus fumigatus* by disk diffusion method. Compound 5b was found to be most effective with largest zone of inhibition.

Key words: Thiazole, Acetophenones, Antibacterial, Antifungal, Substituted Aldehydes.

INTRODUCTION

Thiazole derivatives have attracted a great deal of interest owing to their anticancer activity (Kumar *et al.*, 1993; Timita *et al.*, 2002; Gorczynski *et al.*, 2004), antibacterial activity (Karabasanagouda *et al.*, 2008; Khan *et al.*, 2012), antifungal activity (Karabasanagouda *et al.*, 2008; Khan *et al.*, 2012), anti-inflammatory activity (Karabasanagouda *et al.*, 2008), antitubercular activity (Pattan *et al.*, 2009), cardiotoxic activity (Giridhar *et al.*, 2001), antidegenerative activity on cartilage (Panico *et al.*, 2003) etc. Thiazoles are known to be allosteric enhancer of A₁ adenosine receptors (Goblyos *et al.*, 2005) whereas other analogs are known to be inhibitors of protein phosphatases (Wipf *et al.*, 2001). Heterocycle-bearing substrates are particularly desirable structures for screening and are prevalent in drugs that have reached the market place.

The development of simple and general synthetic routes for widely used organic compounds from readily available reagents is one of the major challenges in organic chemistry. Therefore to meet the facile results of these tough challenges thiazole nucleus was being considered. Among the wide variety of

heterocycles that have been explored for developing pharmaceutically molecules, thiazole derivatives have played a vital role in the medicinal chemistry. There are large numbers of synthetic compounds with thiazole nucleus used for antimicrobial activities when properly substituted at 2-position. In view of these observations and in continuation to develop better and potent antimicrobial agents, some newer thiazole derivatives were synthesized.

METHODOLOGY

Melting points were taken in open capillaries and are uncorrected. IR spectrum of compounds in KBr pellets were recorded on a FTIR-8400S spectrophotometer (SHIMADZU). ¹H NMR spectra of the compounds were recorded on Bruker DRX 300 NMR spectrophotometer in DMSO-d₆ using TMS as internal standard. Mass spectra of the compounds were recorded on MSN-9629 mass spectrometer. Elemental analysis was carried out on Elemental Vario EL III Carlo Erba 1108. The purity of compounds was monitored by thin layer chromatography. Thin layer chromatographic analysis of the compounds were performed on silica gel G coated glass

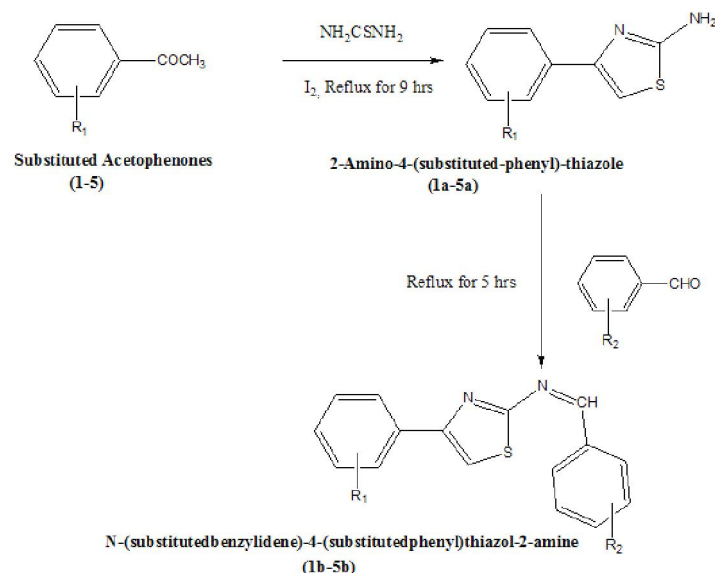


Figure 1. Synthesis of some Schiff bases derived from 2-Aminothiazole derivatives

Compound Number	R ₁	R ₂
1b	H	<i>m</i> -methoxy
2b	H	<i>m</i> -chloro
3b	H	H
4b	H	<i>p</i> -methoxy
5b	<i>o</i> -hydroxy	<i>p</i> -chloro

plates using Chloroform: Methanol: Pet.Ether (9:1:0.5) as mobile phase. The spots were visualized by exposure to iodine vapours.

General method for the synthesis of (1a-5a)

Various substituted acetophenones (**1-5**) (0.01mol) were refluxed with iodine (0.01mol) and thiourea (0.02mol) for 9hrs to get 2-amino-4-(substituted-phenyl)thiazole (**1a-5a**). The solid obtained was washed with diethyl ether, after which it was washed with sodium thiosulfate. Finally, it was washed with water and the residue was filtered, dried and recrystallized from distilled water.

General method for the synthesis of (1b-5b)

2-amino-4-(substituted-phenyl)-thiazole (**1a-5b**) (0.01mol) were refluxed with various substituted aromatic aldehydes (0.01mol) in ethanol along with glacial acetic acid (2-3 drops) for 5 hrs to get N-(substituted-benzylidene)-4-(substituted-phenyl)thiazol-2-

amine (**1b-5b**). The final products were purified by recrystallization from water : DMF (1 : 1).

RESULTS AND DISCUSSION

The synthesis of some Schiff bases derived from 2-Aminothiazole derivatives was shown in figure 1. *N*-(3-methoxybenzylidene)-4-phenylthiazol-2-amine (**1b**): Yield: 55.34 %; m.p. 107-108 °C; Anal. Calcd. for C₁₇H₁₄N₂OS: C, 69.36; H, 4.79; N, 9.52. Found: C, 69.33; H, 4.84; N, 9.47; IR (KBr, cm⁻¹): 3062.28 (C-H stretching of aromatic ring), 2977.4 (=C-H stretching of N=C-H), 2945.76 (-C-H stretching of OCH₃), 1674.86 (C=N stretching of N=C-H), 1586.24 (C-C stretching of aromatic ring), 1227.4 (C-O stretching of -OCH₃), 674.38 (C-S stretching of thiazole); ¹HNMR (DMSO-d₆, δ / ppm): 3.317 (s, 3H, OCH₃), 6.977 (s, 1H, =C-H), 7.087-7.875 (m, 9H, Aromatic), 8.187 (s, 1H, N=C-H). MS (m/z (relative abundance, %)): 294 (M⁺, 28.3), 264, 187 (BP, 100), 134, 133, 108, 104, 77.

Table I. Antibacterial activity of compounds (1b-5b)

Compounds	Zone of Inhibition (mm)		
	<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>
1b.	17.3 ± 0.33	16.3 ± 0.00	17 ± 0.00
2b.	19.2 ± 0.00	20.2 ± 0.00	20.3 ± 0.33
3b.	16.4 ± 0.00	15 ± 0.00	15.5 ± 0.00
4b.	17.3 ± 0.00	17 ± 0.33	17 ± 0.67
5b.	21.5 ± 0.00	20.5 ± 0.00	20.4 ± 0.00
Ciprofloxacin	27 ± 0.00	28 ± 0.00	27 ± 0.00
DMF	-	-	-

All the values are expressed as mean ± SEM of triplicates

Table II. Antifungal activity of compounds (1b-5b)

Compounds	Zone of Inhibition (mm)		
	<i>C. albicans</i>	<i>A. flavus</i>	<i>A. fumigatus</i>
1b.	10.3 ± 0.33	11 ± 0.00	10 ± 0.00
2b.	13.4 ± 0.00	13 ± 0.00	12.2 ± 0.00
3b.	10.3 ± 0.33	9.3 ± 0.33	9.3 ± 0.33
4b.	9.3 ± 0.33	10.7 ± 0.67	11 ± 0.00
5b.	13.5 ± 0.00	14.0 ± 0.00	13.5 ± 0.00
Fluconazole	17 ± 0.00	16 ± 0.00	17 ± 0.00
DMF	-	-	-

All the values are expressed as mean ± SEM of triplicates

N-(3-chlorobenzylidene)-4-phenylthiazol-2-amine (2b): Yield: 63.32 %; m.p. 117-118 °C; Anal. Calcd. for C₁₆H₁₁ClN₂S: C, 64.32; H, 3.71; N, 9.38. Found: C, 64.33; H, 3.69; N, 9.39; IR (KBr, cm⁻¹): 3064.77 (C-H stretching of aromatic ring), 2948.38 (=C-H stretching of N=C-H), 1678.56 (C=N stretching of N=C-H), 1569.38 (C-C stretching of aromatic ring), 776.58 (C-Cl stretching of *m*-chloro), 682.12 (C-S stretching of thiazole); ¹HNMR (DMSO-d₆, δ / ppm): 6.919 (s, 1H, =C-H), 7.057-7.896 (m, 9H, Aromatic), 8.189 ppm (s, 1H, N=C-H). MS (m/z (relative abundance, %)): 300 (M+2), 298 (M+, 31.6), 265, 187 (BP, 100), 138, 134, 133, 112, 77.

Synthesis of *N*-benzylidene-4-phenylthiazol-2-amine (3b): Yield: 58.58 %; m.p. 110-111 °C; Anal. Calcd. for C₁₆H₁₂N₂S: C, 72.70; H, 4.58; N, 10.60. Found: C, 72.72; H, 4.56; N, 10.62; IR (KBr, cm⁻¹): 3053.11 (C-H stretching of aromatic ring), 2961.88 (C-H stretching of N=C-H), 1623.95 (C=N stretching of N=C-H), 1525.59 (C-C stretching of aromatic ring),

628.86 (C-S stretching of thiazole); ¹HNMR (DMSO-d₆, δ / ppm): 6.588 (s, 1H, =C-H), 7.195-7.394 (m, 10H, Aromatic), 8.188 ppm (s, 1H, N=C-H); MS (m/z (relative abundance, %)): 264 (M+, 37.4), 187 (BP, 100), 134, 133, 104, 77.

Synthesis of *N*-(4-methoxybenzylidene)-4-phenylthiazol-2-amine (4b): Yield: 66.41 %; m.p. 111-112 °C; Anal. Calcd. for C₁₇H₁₄N₂OS: C, 69.36; H, 4.82; N, 9.52. Found: C, 69.34; H, 4.81; N, 9.51; IR (KBr, cm⁻¹): 3060.82 (C-H stretching of aromatic ring), 2977.89 (C-H stretching of N=C-H), 2906.53 (C-H stretching of OCH₃), 1662.52 (C=N stretching of N=C-H), 1581.52 (C-C stretching of aromatic ring), 1240.14 (C-O stretching of OCH₃), 653.82 cm⁻¹ (C-S stretching of thiazole); ¹HNMR (DMSO-d₆, δ / ppm): 3.311 (s, 3H, OCH₃), 6.907 (s, 1H, =C-H), 7.084-7.825 (m, 9H, Aromatic), 8.188 ppm (s, 1H, N=C-H). MS (m/z (relative abundance, %)): 294 (M+, 28.3), 264, 187 (BP, 100), 134, 133, 108, 104, 77.

Synthesis of 2-(2-(4-Chlorobenzylideneamino)thiazol-4-yl)phenol (5b): Yield: 67.68 %; m.p. 125-126 °C; Anal. Calcd. for C₁₆H₁₁ClN₂OS: C, 61.05; H, 3.52; N, 8.90. Found: C, 61.01; H, 3.55; N, 8.89; IR (KBr, cm⁻¹): 3060.82 (C-H stretching of aromatic ring), 2977.89 (C-H stretching of N=C-H), 2906.53 (C-H stretching of OCH₃), 1662.52 (C=N stretching of N=C-H), 1581.52 (C-C stretching of aromatic ring), 1240.14 (C-O stretching of C-OH), 770.45 (C-Cl stretching of *p*-chloro), 653.82cm⁻¹ (C-S stretching of thiazole); ¹HNMR (DMSO-d₆, δ / ppm): 4.480 (s, 1H, OH), 6.103 (s, 1H, =C-H), 6.327-7.777 (m, 8H, Aromatic), 8.458ppm (s, 1H, N=C-H). MS (m/z (relative abundance, %)): 316 (M+2), 314 (M+, 21.4), 203 (BP, 100), 150, 149, 138, 112, 77.

Antimicrobial activity

The synthesized compounds 1-5 were screened for antibacterial (*S. aureus*, *E. coli*, *P. aeruginosa*) and antifungal (*C. albicans*, *A. flavus*, *A. fumigatus*) activities by disk diffusion method at a concentration of 2 mg/mL using DMF as a solvent. The results were recorded in duplicate using Ciprofloxacin and Fluconazole as standards and are given in table I and II.

Various substituted acetophenones (1-5) reacted with iodine and thiourea to get 2-Amino-4-(substituted-phenyl)-thiazole (Sutariya *et al.*, 2007) (1a-5a). Next, 2-amino-4-(substituted-phenyl)-thiazole (1a-5a) reacted with various substituted aldehydes to get N-(substitutedbenzylidene)-4-(substitutedphenyl)thiazol-2-amine (1b-5b). In this reaction, amino group of thiazole (1a-5a) was treated with various aromatic aldehydes to get corresponding Schiff's bases (1b-5b). The FTIR spectra of compounds 1b-5b exhibited bands in the region of 2948.38-2977.89 cm⁻¹ due to C-H stretching of N=C-H. In ¹H NMR spectra of compounds 1b-4b, one proton singlet appeared between δ 8.187-8.458 ppm was assigned to N=C-H proton. MS of representative compounds 1b-5b exhibited molecular ion peak at m/z.

The structures of the synthesized compounds were assigned on the basis of elemental analysis, ¹H NMR, FTIR and Mass spectral data and physical data. The synthesized compounds were screened for antibacterial and antifungal activity against *Staphylococcus aureus*,

Escherichia coli, *Pseudomonas aeruginosa*, *Candida albicans*, *Asperigillus flavus* and *Asperigillus fumigatus* by disk diffusion method. In Scheme-1, compound 5b was found to be most effective with the largest zone of inhibition against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Candida albicans*, *Asperigillus flavus* and *Asperigillus fumigates*. Compound 2b was also found to be very effective against all the microorganisms after compound 5b. Compound 1b and 4b were also reported with the significant activities against the tested microorganisms.

CONCLUSION

Both analytical and spectral data (IR, ¹H-NMR, MS) of all the synthesized compounds were in full agreement with the proposed structure. After comparing the antimicrobial results of compounds 5a-5b, it was concluded that compound 5b was found to possess maximum activity against tested strains. This maximum activity may be due to presence of both hydroxy and chloro group in compound 5b.

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