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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, ^{1}H 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), anti-tubercular activity (Pattan *et al*., 2009), cardio-tonic activity (Giridhar *et al*., 2001), anti-degenerative activity on cartilage (Panico *et al*., 2003) etc. Thiazoles are known to be allosteric enhancer of A_1 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.

MATERIAL AND METHODS

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). ^{1}HNMR spectra of the compounds were recorded on Bruker DRX 300 NMR spectrophotometer in DMSO-d_6 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.

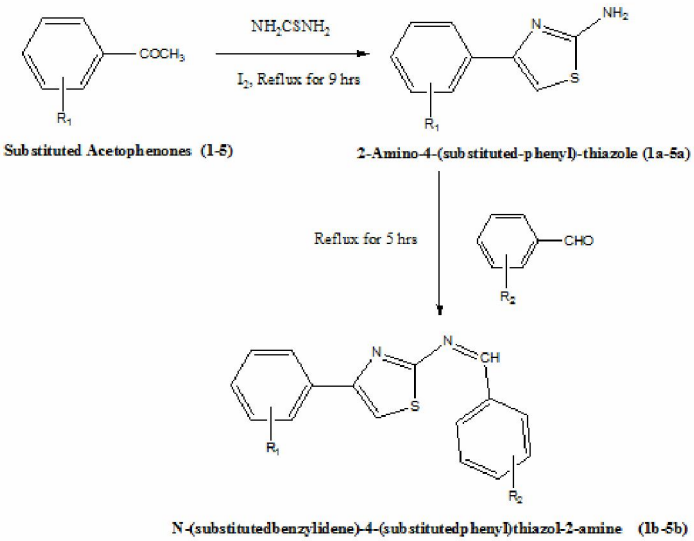

Figure 1. Synthetic pathway

Table I. Derivation of the compound

Where:	Compound Number	R_1	R_2
	1b	H	*m*-methoxy
	2b	H	*m*-chloro
	3b	H	H
	4b	H	*p*-methoxy
	5b	*o*-hydroxy	*p*-chloro

Thin layer chromatographic analysis of the compounds were performed on silica gel G coated glass 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 9 hrs 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).

N-(3-methoxybenzylidene)-4-phenyl-thiazol-2-amine **(1b):** Yield: 55.34 %; m.p. 107-108 ºC; Anal. Calcd. for $C_{17}H_{14}N_2OS$: 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 OCH_3), 1674.86 (C=N stretching of N=C-H), 1586.24 (C-C stretching of aromatic ring), 1227.4 (C-O stretching of –OCH_3), 674.38 (C-S stretching of thiazole); ^{1}HNMR (DMSO-d_6, δ / ppm): 3.317 (s, 3H, OCH_3), 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.

N-(3-chlorobenzylidene)-4-phenyl-thiazol-2-amine **(2b):** Yield: 63.32 %; m.p. 117-118 ºC; Anal. Calcd. for $C_{16}H_{11}ClN_2S$: 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); ^{1}HNMR (DMSO-d_6, 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-phenyl-thiazol-2-amine* (3b):** Yield: 58.58 %; m.p. 110-111 ºC; Anal. Calcd. for $C_{16}H_{12}N_2S$: 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); ^{1}HNMR (DMSO-d_6, 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-methoxybenzyli-dene)-4-phenylthiazol-2-amine* (4b):** Yield: 66.41 %; m.p. 111-112 ºC; Anal. Calcd. for $C_{17}H_{14}N_2OS$: 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 OCH_3), 1662.52 (C=N stretching of N=C-H), 1581.52 (C-C stretching of aromatic ring), 1240.14 (C-O stretching of OCH_3), 653.82 cm^{-1} (C-S stretching of thiazole); ^{1}HNMR (DMSO-d_6, δ / ppm): 3.311 (s, 3H, OCH_3), 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-Chlorobenzyli-deneamino)thiazol-4-yl)phenol* (5b):** Yield: 67.68 %; m.p. 125-126 ºC; Anal. Calcd. for $C_{16}H_{11}ClN_2OS$: 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 OCH_3), 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), 653.82 cm^{-1} (C-S stretching of thiazole); ^{1}HNMR (DMSO-d_6, δ / ppm): 4.480 (s, 1H, OH), 6.103 (s, 1H, =C-H), 6.327-7.777 (m, 8H, Aromatic), 8.458 ppm (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 2mg/mL using DMF as a solvent. The results were recorded in duplicate using ciprofloxacin and fluconazole as standards and are given in table II and III.

RESULTS AND DISCUSSION

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 2948.38-2977.89cm^{-1} due to C-H stretching of N=C-H. In ^{1}H NMR spectra of compounds **1b-4b**, one proton singlet appeared between δ 8.187-8.458ppm 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, ^{1}H 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, Aspergillus flavus and Aspergillus fumigatus* by disk diffusion method. In figure 1, compound **5b** was found to be most effective with the largest zone of inhibition against *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida albicans, Aspergillus flavus and Asperigillus fumigates*. Compound **2b** was also found to be very effective against all the

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

Compounds	Zone of Inhibition (mm)		
	S. aureus	***E. coli***	***P. aeruginosa***
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 III. Antifungal activity of compounds (1b-5b)

Compounds	Zone of Inhibition (mm)		
	C. albicans	***A. flavus***	***A. fumigatus***
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

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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