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

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Submitted: 15-11-2012
Revised: 20-01-2013
Accepted: 16-03-2013

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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), cardiotonic activity (Giridhar et al., 2001), anti-degenerative 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.

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). 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 plates using Chloroform: MeOH: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.

<table>
<thead>
<tr>
<th>Where:</th>
<th>Compound Number</th>
<th>R₁</th>
<th>R₂</th>
</tr>
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<tbody>
<tr>
<td>1b</td>
<td></td>
<td>H</td>
<td>m-methoxy</td>
</tr>
<tr>
<td>2b</td>
<td></td>
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<tr>
<td>5b</td>
<td></td>
<td>o-hydroxy</td>
<td>p-chloro</td>
</tr>
</tbody>
</table>

**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 °C; Anal. Calcd. for C₁₇H₁₄N₂O: 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=C 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+), 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 °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-S stretching of thiazole); ¹HNMR (DMSO-d₆, δ / ppm): 3.317 (s, 3H, OCH₃), 6.919 (s, 1H, =C-H), 7.057-7.896 (m, 9H, Aromatic), 8.189 (s, 1H, N=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, 112, 77.

Synthesis of N-benzylidene-4-phenylthiazol-2-amine (3b): Yield: 58.58 %; m.p. 110-111 ºC; Anal. Calcd. for C$_{16}$H$_{12}$N$_2$S: 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), 2916.88 (C-H stretching of N=C-H), 2977.89 (C-H stretching of N=C-H), 2906.53 (C-H stretching of aromatic ring), 1662.52 (C=N stretching of aromatic ring), 2948.38-2977.89 cm$^{-1}$ due to C-H stretching of N=C-H. In $^1$H NMR spectra of 1b-5b, one proton singlet appeared between δ 8.187-8.458 ppm was assigned to N=C-H proton. 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 ºC; Anal. Calcd. for C$_{16}$H$_{14}$N$_2$OS: 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, 104, 77.

Synthesis of 2-(2-(4-Chlorobenzylidene)amino)thiazol-4-yl)phenol (5b): Yield: 67.68 %; m.p. 125-126 ºC; Anal. Calcd. for C$_{20}$H$_{15}$ClN$_2$: 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 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 & II.

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 2948.38-2977.89 cm$^{-1}$ due to C-H stretching of N=C-H. In $^1$H NMR spectra of compounds 1b-4b, one proton singlet appeared between δ 8.187-8.458 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, $^1$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 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, Aspergillus flavus and Aspergillus fumigatus. 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.

ACKNOWLEDGEMENT

The authors are thankful to IIT, Delhi and CDRI, Lucknow for providing facilities.

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