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Synthesis and Biological Activity of Newly Synthesized Schiff Bases Containing Benzothiazole Moiety

T. U. Kendre[1]*, M.A. Basser[2] and P.A. Kulkarni[2]

1P.G. Department of Chemistry, Toshniwal A.C.S. College, Sengaon

2P. G. Department of Chemistry, Yeshwant Mahavidyalaya, Nanded.

Abstract:

The current study highlights the synthesis of newly synthesized Schiff bases containing benzothiazole moiety. The Schiff bases have been synthesized by using various halo substituted aldehydes under acidic conditions. These synthesized compounds are characterized by IR, ^{1}H NMR, UV visible, and Mass spectroscopy. The synthesized compounds were evaluated for antibacterial on two strains (Escherichia coli, Staphylococcus aureus,) and antifungal activity on two strain (Candia crusei, Candida albicans) using agar well diffusion method. Moreover, all the synthesized compounds shows excellent antibacterial activity and antifungal activity.

Key words: Schiff base, benzothiazole, antibacterial, antifungal.

Introduction:

In 1887, 2-substituted benzothiazole was first synthesized by A.W. Hofmann then because of different activity as well as simple cyclization mechanism and number of synthetic routes has been reported. 2-Substitued benzothiazole has emerged in its usage as a core structure in the diversified therapeutically applications. Nitrogen and sulfur containing benzothiazole compounds are attracting class of organic compounds and had a considerable interest of many researchers due to their wide range of pharmacological activities. Benzothiazole derivatives were attracted considerable interest of many authors due to their biological activities including antimicrobial[1], antiviral[2], antitubercular[3] and anti-inflammatory[4]. In addition they have motivating characteristics for application of photochromism and theromochromism[5] in both states. Moreover benzothiazole derivatives containing nitrogen and sulfur atoms acting as a drug and identified as an antioxidant inhibitor[6]as well as surface active chelating agents[7]. Schiff bases containing benzothiazole used for various diseases, such as neurodegenerative disorders, local it has been useful therapeutically in the treatment of certain diseases such as cerebral ischemia, central muscle relaxants and cancer[8]. In addition Schiff base complexes possess a wide range of bioactivities and their chemistry, analytical, agricultural, industrial uses as catalyst and pharmacological applications have been extensively investigated [9-11]. Formation of Schiff base generally takes place under acid or base catalysis or with heat. Bases obtained from amines and aldehydes have applications in various disciplines of chemistry. Several of these biomimetic Schiff bases are

gifted with antimicrobial and antitumor properties and could be used against HIV[12-13]. Some authors reported Schiff bases of benezothiazole- trizole derivative compounds and evaluated for their antimicrobial activities against bacterial and fungal stain and they concluded that all derivatives of Schiff bases of benzothiazole-triazole antimicrobial activity increases with p- substitution[14.]

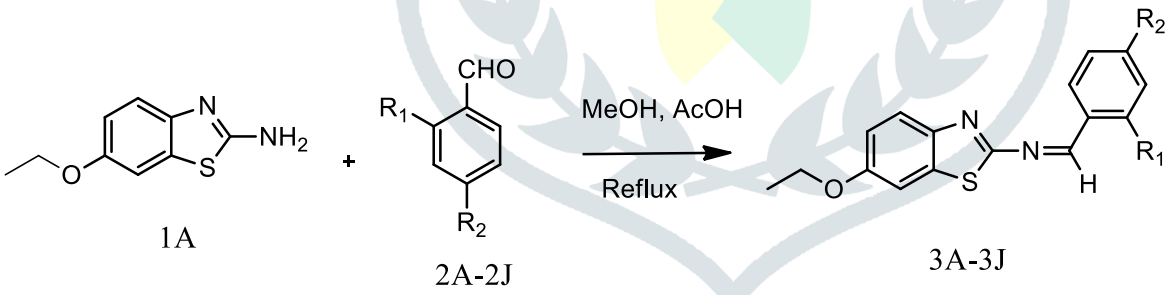
Experimental:

1. **Materials and equipment**:

All chemicals are of analytical grade purchased from Sigma Aldrich and used as received without any further purification. The required solvents used are from SD Fine chemicals Ltd. Multiple techniques and devices were used for synthesis of Schiff bases. Among these techniques, thin layer chromatography (TLC), FT-IR, ^{1}H NMR, Mass spectroscopy, UV visible spectroscopy. Then, all compounds were screened for antibacterial on two strains (Staphylococcus aureus, Escherichia Coli) and antifungal activity on two strain (Candia crusei, Candida albicans) using agar well diffusion method.

2. **General method for Synthesis of Schiff base ligands**:

An equimolar mixture of 6-ethoxybenzo[d]thiazol-2-amine (1:1 mole ratio) (1A, 0.001 m) and 4-chloro-2-hydroxybenzaldehyde 2A (0.001 m) in methanol (15mL) containing glacial acetic acid (0.5mL) was refluxed for 3h. After completion of reaction the reaction mass poured on crushed ice, crude product was formed, then the crude product was recrystallized with ethanol. The formed crude product was washed 2-3 times with dilute acetic acid for the purity of product. Excess of solvent was distilled off and residue was kept in cold. The solid was filtered and recrystallized from acetic acid.



Scheme 1. Preparation procedure for the syntheses of Schiff base ligands

Table 1. The different derivatives of Schiff base ligands.

Sr. no.	Compounds	R_1	R_2
1.	3A	-OH	-Cl
2.	3B	-OH	-Br
3.	3C	-OH	-I
4.	3D	-OH	-F

5.	3E	-OH	$-OCH_3$
6.	3F	-Cl	-Cl
7.	3G	-Cl	-Br
8.	3H	-Cl	-I
9.	3I	-Cl	-F
10.	3J	-Cl	$-OCH_3$

Spectral data of synthesized compounds:

3A: 5-chloro-2-(((6-ethoxybenzo[d]thiazol-2-yl)imino)methyl)phenol: Yellow solid, m.p. 216°C. IR (cm^{-1}): 3352 (N-H), 1625 (C=N), 3638 (Ar-OH), 1257 (C-O). ^{1}H NMR (500 MHz) δ9.23 (1H, s, Ar-OH), δ8.48 (1H, s, N=CH), δ7.01-7.53 (6H, m, Ar-H), δ4.13 (2H, q) and δ1.43 (3H, t). LCMS m/z (%) 333 (100%) [M^{+1}].

3B: 5-bromo-2-(((6-ethoxybenzo[d]thiazol-2-yl)imino)methyl)phenol: M.P. 180ºC. IR cm^{-1} (KBR): 3429 (N-H), 1629 (C=N), 3641 (Ar-OH), 1260 (C-O). ^{1}H NMR studies ($CDCl_3$) ppm: δ9.46 (1H, s, Ar-OH), δ8.40 (1H, s, N=CH), δ7.01-7.91 (6H, m, Ar-H), δ4.11 (2H, q) and δ1.49 (3H, t). LCMS m/z (%) 378.8 (100%) [M^{+1}].

3C: 2-(((6-ethoxybenzo[d]thiazol-2-yl)imino)methyl)-5-iodophenol : M.P. 154ºC. IR cm^{-1} (KBR): 3430 (N-H), 1630 (C=N), 3639 (Ar-OH), 1254 (C-O). ^{1}H NMR studies (CDCl3) ppm: δ9.42 (1H, s, Ar-OH), δ8.28 (1H, s, N=CH), δ7.00-7.81 (6H, m, Ar-H), δ4.09 (2H, q) and δ1.34 (3H, t). LCMS m/z (%) 425.3 (100%) [M^{+1}].

3D: 2-(((6-ethoxybenzo[d]thiazol-2-yl)imino)methyl)-5-fluorophenol: M.P. 210ºC. IR cm^{-1} (KBR): 3427 (N-H), 1632 (C=N), 3641 (Ar-OH), 1255 (C-O). ^{1}H NMR studies (CDCl3) ppm: δ8.73 (1H, s, Ar-OH), δ8.52 (1H, s, N=CH), δ6.60-7.59 (6H, m, Ar-H), δ4.15 (2H, q) and δ1.39 (3H, t). LCMS m/z (%) 317.4 (100%) [M^{+1}].

3E: 2-(((6-ethoxybenzo[d]thiazol-2-yl)imino)methyl)-5-methoxyphenol: M.P. 253ºC. IR cm^{-1} (KBR): 3412 (N-H), 1628 (C=N), 3643 (Ar-OH), 1257 (C-O). ^{1}H NMR studies (CDCl3) ppm: δ8.73 (1H, s, Ar-OH), δ8.52 (1H, s, N=CH), δ6.60-7.59 (6H, m, Ar-H), δ4.15 (2H, q), δ3.78 (3H, S, OCH_3) and δ1.39 (3H, t). LCMS m/z (%) 329.4 (100%) [M^{+1}].

3F: N-(2,4-dichlorobenzylidene)-6-ethoxybenzo[d]thiazol-2-amine: m.p. 198°C. IR cm^{-1}: 3342 (N-H), 1628 (C=N), 1260 (C-O). ^{1}H NMR (500 MHz), δ8.52 (1H, s, N=CH), δ7.00-7.54 (6H, m, Ar-H), δ4.10 (2H, q) and δ1.28 (3H, t). LCMS m/z (%) 352.3 (100%) [M^{+1}].

3G: N-(4-bromo-2-chlorobenzylidene)-6-ethoxybenzo[d]thiazol-2-amine: m.p. 208°C. IR cm^{-1}: 3305 (N-H), 1632 (C=N), 1256 (C-O). ^{1}H NMR (500 MHz), δ8.42 (1H, s, N=CH), δ7.00-7.84 (6H, m, Ar-H), δ4.10 (2H, q) and δ1.12 (3H, t). LCMS m/z (%) 396.7 (100%) [M^{+1}].

3H: N-(2-chloro-4-iodobenzylidene)-6-ethoxybenzo[d]thiazol-2-amine: m.p. 212°C. IR cm^{-1}: 3318 (N-H), 1626 (C=N), 1259 (C-O). ^{1}H NMR (500 MHz), δ8.53 (1H, s, N=CH), δ7.00-7.94 (6H, m, Ar-H), δ4.10 (2H, q) and δ1.12 (3H, t). LCMS m/z (%) 443.7 (100%) [M^{+1}].

3I: N-(2-chloro-4-fluorobenzylidene)-6-ethoxybenzo[d]thiazol-2-amine: 220°C. IR cm^{-1}: 3318 (N-H), 1626 (C=N), 1257 (C-O). ^1H NMR (500 MHz), δ8.86 (1H, s, N=CH), δ7.00-7.78 (6H, m, Ar-H), δ4.15 (2H, q) and δ1.35 (3H, t). LCMS m/z (%) 335.8 (100%) $[M^{+1}]$.

Results and Discussion:

1. Characterizations of Schiff Base ligands:

The rout for the synthesis of Schiff base ligand by using amine and various aldehydes in methanol as a solvent under reflux condition in presence of 0.5ml of glacial acetic acid. After completion of reaction the reaction mass poured on crushed ice, crude product was formed then the crude product was recrystallized with ethanol. Moreover, the morphological studies was evaluated by using various analytical techniques like FTIR, ^1H NMR, Mass Spectroscopy, UV Visible spectroscopy and applied for the biological studies including antimicrobial and antifungal.

The spectra of all synthesized compounds were evaluated by using FT-IR. The FTIR spectra of all the synthesized compounds are nearly same to each other. It shows the vibrational peak at 1627 cm^{-1} is related to the stretching frequency of the imine group (C=N) and the observed peak at 1377 cm^{-1} and 721 cm^{-1} may be due to the (C-N) and (C-S-C) respectively. The two peak at 3639 cm^{-1}, 1257 cm^{-1} were attributed due to the (Ar-OH) and (C-O) respectively.

The electronic spectra of all the synthesized compounds were studied by using UV Visible spectroscopy. It shows intense absorption peak in between the range 307 – 451 nm is due to the (π-π^*) and (n-π^*) transition. The absorption data of all the synthesized Schiff base ligands are nearly similar with each other.

2. Biological activities of Schiff base ligands

The antibacterial activities of the different Schiff bases (3A-J) were determined by agar well diffusion method[15]. The compounds were estimated for antibacterial activity against Escherichia coli [MTCC 8742] and Staphylococcus aureus [MTCC 6535]. Again, the antifungal activity performed against Candia crusei [MTCC 14264] and Candida albicans [MTCC 64558] were procured in microbiology department, YM, Nanded, India. The minimum inhibitory concentrations (MIC's) values were determined for bacterial and fungal activity respectively, as shown in **Table 2**.

All the synthesized schiff bases derivatives (**3A-J**) were screened for their *in vitro* antimicrobial activity and showed good inhibitory activity at 10.5µg/mL, 12.5µg/mL & 25µg/mL concentration. Antimicrobial activity tested against Escherichia coli (MTCC 8742), Staphylococcus aureus (MTCC 6535), and antifungal activity against Candia crusei (MTCC 14264) Candida albicans (MTCC 64558). The results of these studies in terms of zone of inhibition (ZOI) and minimum inhibitory concentrations (MICs) are summarized in **Table 2.** The compounds **3A**, **3B**, **3C**, **3G**, **3H**, **3I**, shows good to moderate activity. The compounds **3D**, **3E**, **3F**, **3J** showed sharp decrease in activity. Thus newly synthesized Schiff bases which has activating functional group –Cl, -Br and –I showed antimicrobial inhibitory activity when compared with standard drug. The remaining compounds showed nearly equal inhibition activity.

Table 2: - Antimicrobial and antifungal activity of different Schiff bases 3A-J (MIC µg/mL).

Sr. No.	Entry	Zone of inhibition in mm			
		E. coli MTCC 8742	S. aureus MTCC 6535	C. crusei MTCC 14264	C. albicans MTCC 64558
1.	**3A**	26(10.5)	27(10.5)	24(25)	26(25)
2.	**3B**	27(10.5)	28(<10.5)	25(25)	25(25)
3.	**3C**	25(12.5)	26(12.5)	27(25)	24(25)
4.	**3D**	08(<200)	06(<200)	09(<200)	07(<200)
5.	**3E**	06(<200)	05(<200)	07(<200)	06(<200)
6.	**3F**	04(<200)	08(<200)	05(<200)	03(<200)
7.	**3G**	28(10.5)	26(12.5)	27(25)	26(25)
8.	**3H**	26(12.5)	25(12.5)	28(25)	27(25)
9.	**3I**	30(<10.5)	32(<10.5)	28(25)	30(25)
10.	**3J**	03(<200)	06(<200)	04(<200)	05(<200)

Conclusion:

In the present work, we have successfully synthesized new Schiff bases containing benzothiazole moiety by using amine and different halo substituted aldehydes. Then, for the confirmation of the morphological structure the synthesized Schiff base ligands were characterized by using the NMR, IR, UV spectra and Mass spectroscopy. Moreover, the newly synthesized compounds were evaluated for antibacterial on two strains (Escherichia coli, Staphylococcus aureus,) and antifungal activity on two strain (Candia crusei, Candida albicans) using agar well diffusion method. The newly synthesized compounds **3A**, **3B**, **3C**, **3G**, **3H**, **3I**, shows good to moderate activity. The compounds **3D**, **3E**, **3F**, **3J** showed sharp decrease in activity. Thus synthesized Schiff bases which has activating functional group –Cl, -Br and –I showed antimicrobial inhibitory activity when compared with standard drug. The remaining compounds showed nearly equal inhibition activity.

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