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Synthesis, Characterization, and Antimicrobial Activity of Schiff Bases Derived From 4, 6 - Difluoro - 2 - Amino Benzothiazole

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Abstract

Some novel Schiff bases namely *N-(4-(dimethyl amino)benzylidene)-4,6-difluoro benzothiazole-2-amine*; *4-bromo-2-(((4,6-difluoro benzothiazole-2-yl) imino) methyl)phenol* and *N-(3,4-dimethoxybenzylidene)-4,6-difluoro benzothiazole-2-amine* have been synthesized from condensation reaction of 4,6-difluoro-2-amino benzothiazole with different aromatic aldehydes like *4-(dimethyl amino)benzaldehyde, 5-bromo-2-hydroxy benzaldehyde* and *3,4-dimethoxy benzaldehyde* . The synthesized Schiff bases were characterized by elemental analysis, FT-IR, Mass and ^{1}H NMR spectroscopy. Antimicrobial and Antifungal activities of these Schiff bases were tested using MIC determination against gram positive (*S. Aureus, B.Subtilis),* gram negative bacteria *(S. Marcescens, E. Coli)* and *Rhizopus sp. and A. Niger*.

Keywords

Schiff base, Benzothiazole derivative, Antimicrobial activity, Antifungal activity, MIC determination.

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1. INTRODUCTION

Schiff bases derived from an amine and aldehyde are an important class of ligands in coordination chemistry [1,2] that have been studied extensively. They were first reported by a German chemist Hugo Schiff [3] Nobel Prize winner in 1864. Schiff bases are characterized by imine or azomethine group (-CH=N) [4] and their general structural formula is R_1-CH=N-R_2 where R_1 and R_2 are alkyl, aryl or heterocyclic group having different substituents. Schiff bases coordinate to transition metal ions [5-9] via azomethine nitrogen and these complexes are play an important role in the development of coordination chemistry [10]. Presence of azomethine group helps to explain the mechanism of racemization and transamination reaction occurred in biological system [11]. Schiff bases play very important role in industrial and biological field. They are biological active compounds and possess many biological activities such as anticancer [12], anti-tuberculosis [13], antibacterial [14], antimicrobial [15], plant growth inhibitors [16] and anti-inflammatory activity [17].

Benzothiazoles are heterocyclic bicyclic ring containing nitrogen and sulfur heteroatoms in five membered ring and its ring made from 1,3-thiazole

ring fused with benzene ring. These moieties are found large number of interests in medicinal and pharmaceutical field [18,19,20,21] due to their biological applications. Various substituted benzothiazoles have shown pharmacological activities such as antitumor [22,23], antimicrobial [24], antibacterial [25,26], antifungal [27], anti-inflammatory [28], anticonvulsive [29], analgesic [30] and Parkinson's disease [31].

Due to their importance in pharmaceutical utilities, in the present work, synthesis of Schiff base from benzothiazole derivative amine is of considerable interest. Apart from biological applications these Schiff bases have another area of applications as corrosion inhibitor [32], dye manufacture [33], perfumery [34] , plant growth regulators[35] and in analytical chemistry where some of these Schiff base compounds were used as ligand in complexometry [36] and intermediate for various synthesis[37,38].

Here an attempt has been made to synthesize and characterize novel Schiff bases derived from 4,6-difluoro benzothiazole. The biological activity of these new synthesized compounds were tested against two gram positive bacteria *S. Aureus, B.Subtilis* and two Gram negative bacteria *i.e. S. Marcescens, E. Coli* and fungal strains *Rhizopus sp.* and *A. Niger* in solvent DMF/$CHCl_3$.

2.EXPERIMENTAL

2.1 Chemicals and reagents:

All starting materials, reagents and other chemicals were obtained from Sigma-Aldrich and used as received. Silica gel and fluorescence active TLC plates (F-2009) were purchased from E.Merck. All the solvents employed for synthesis were commercially available (AR grade) and used as received without further purification.

2.2 Instrument

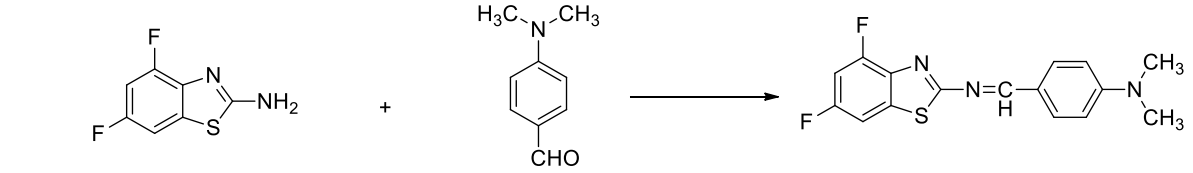
The melting points (uncorrected) were determined using capillary and theils tube filled with paraffin oil. Samples for infrared spectra were prepared as KBr pallets; spectra were recorded on tensor Bruker 27 (Ettlingen, Germany) and expressed in cm^{-1}. Mass spectra (GC-MS) were determined using Jeol D-300 spectrometer**.** NMR spectra were recorded on a model DPX 200 MHz and Advance II 500 MHz Bruker FT-NMR instruments (Ettlingen, Germany).

Elemental analysis data are in accordance with the theoretically calculated percentage of C, H, N and S. Percentage of C, H, N and S were derived using CHN/S/O Analyzer, Perkin Elmer, series11, 2400.

2.3. Synthesis of Schiff base

[A] Synthesis of N-(4-(dimethyl amino) benzylidene)-4,6-difluoro benzothiazole-2-amine

To a methanolic solution of 4,6-difluoro-2-amino benzothiazole (0.186gm,0.001mol) with 4-(dimethyl amino) benzaldehyde (0.149gm, 0.001 mol) was mixed using catalytic amount of glacial acetic acid. The reaction mixture was refluxed with constant stirring at 50-60˚C for 10-12 hrs. Schiff base was obtained by slow evaporation method at room temperature. To remove excess aldehyde, the product was washed with sodium bisulphite and then washed with chilled methanol to remove other impurities. The product was isolated, dried by ether and recrystallized from hot methanol. Yield: 62.95%. **(Scheme-1)** The Schiff base ligand exists in crystalline form and golden yellow in color.



4,6-difluorobenzothiazol-2-amine 4-(dimethylamino)benzaldehyde **DBT-I**

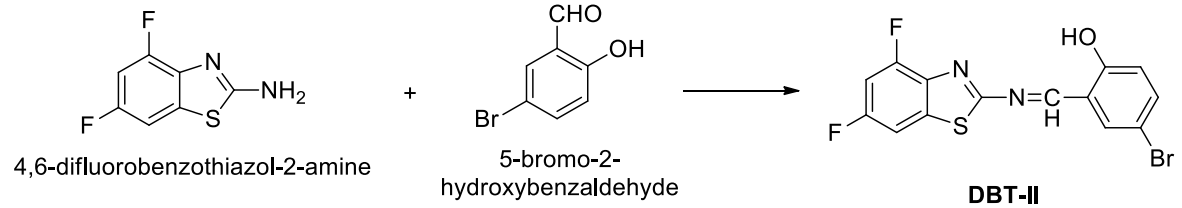
Scheme-1

For $C_{16}H_{13}F_2N_3S$, Melting point is 152-155˚C and Elemental analysis data found: %C 60.45; %H 4.15; %N 13.1; %S 9.98. In FT-IR, bands observed are at 1610 cm^{-1} ν (HC=N, azomethine group), 2815 cm^{-1} ν -$N(CH_3)_2$,1252 cm^{-1} ν(C-F), 722cm^{-1} ν(C-S-C). ^{1}H-NMR (500 MHz, $CDCl_3$): δN-$(CH_3)_2$, 1.63 (s, 6H); δAr-H, 6.85-7.65 (d, 6H); δN=CH, 9.26 (s, 1H) (**SI 1**) and Mass spectra (GC-MS) *m/z* values of **DBT-I** correspond to the M^- adduct (317) are shown in **SI 2** respectively**.**

[B] Synthesis of 4-bromo-2-(((4,6-difluoro benzothiazole-2-yl) imino) methyl) phenol

To a methanolic solution of 4,6-difluoro-2-amino benzothiazole (0.186gm,0.001mol) with 5-bromo-2-hydroxy benzaldehyde (0.201 gm, 0.001 mol) was mixed using catalytic amount of glacial acetic acid. The reaction mixture was refluxed with constant stirring at 50-60˚C for 10-12 hrs. Schiff base was obtained by slow evaporation method at room temperature. To remove excess aldehyde, the product was washed with sodium bisulphite and then washed with chilled methanol to remove other

impurities. The product was isolated, dried by ether and recrystallized from hot methanol. Yield: 78.65%.



4,6-difluorobenzothiazol-2-amine

5-bromo-2-hydroxybenzaldehyde

DBT-II

Scheme-2

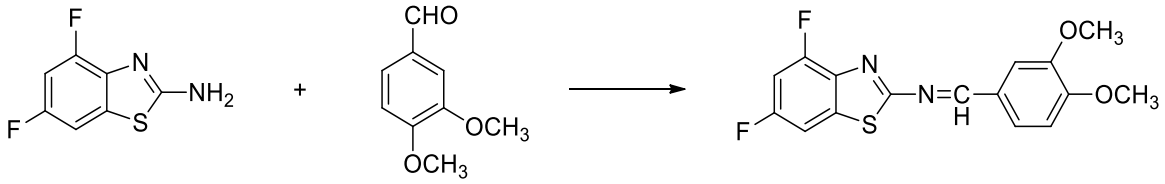
For $C_{14}H_7BrF_2N_2OS$, Melting point is 178-180˚C and Elemental analysis data found: %C 45.22; %H 1.93; %N 7.48; %S 8.55. In FT-IR, bands observed are at 1604 cm^{-1} ν(HC=N, azomethine group), 3127 cm^{-1} ν(OH), 1226 cm^{-1} ν(C-F), 753 cm^{-1} ν(C-S-C). ^{1}H-NMR (500 MHz, $CDCl_3$): δAr-H, 6.82-7.13 (d, 5H); δN=CH, 7.26 (s, 1H); δAr-OH , 5.72 (s, 1H) (**SI 3**) and Mass spectra (GC-MS) *m/z* values of **DBT-II** correspond to the M^- adduct (368), is shown in **SI 4** respectively.

(Scheme-2) The Schiff base ligand exists in amorphous form and yellow in color.

To a methanolic solution of 4,6-difluoro-2-amino benzothiazole (0.186gm,0.001mol) with 3,4-dimethoxy benzaldehyde (0.166 gm, 0.001 mol) was mixed using catalytic amount of glacial acetic acid. The reaction mixture was refluxed with constant stirring at 30-40˚C for 5-7hrs. Schiff base was obtained by slow evaporation method at room temperature. To remove excess aldehyde, the product was washed with sodium bisulphite and then washed with chilled methanol to remove other impurities. The product was isolated, dried by ether and recrystallized from hot methanol. Yield: 55.39%.

[C] Synthesis of N-(3,4-dimethoxybenzylidene)-4,6-difluoro benzothiazole-2-amine

(Scheme-3) The Schiff base ligand exists in crystalline form and pale yellow in color.



4,6-difluorobenzothiazol-2-amine

3,4-dimethoxybenzaldehyde

DBT-III

Scheme-3

For $C_{16}H_{12}F_2N_2O_2S$, Melting point is 192-194 ˚C. Elemental analysis data found: %C 57.62; %H 3.60; %N 8.15; %S 9.45. In FT-IR, bands are observed at 1611 cm^{-1} ν (HC=N, azomethine group), 1226 cm^{-1} ν(C-F), 751 cm^{-1} ν(C-S-C). ^{1}H-NMR (500 MHz, $CDCl_3$): δAr(-OCH_3)$_2$, 3.95 & 3.98 (s, 6H); δAr-H, 6.81-7.10 (d, 5H); δN=CH, 7.14 (s, 1H) **(SI 5)** and Mass spectra (GC-MS) m/z values of **DBT-III** correspond to the M-adduct (335), is shown in **SI 6** respectively.

3. RESULTS AND DISCUSSION

3.1. Spectral studies of ligands

The novel Schiff base compound DBT-I, DBT-II and DBT-III are synthesized according to described process in scheme-1,2 and 3 respectively. The structure of all the compounds were evaluated on the basis of elemental analysis, FT-IR, mass and ^{1}H NMR spectral data. The ligands were insoluble in water but soluble in methanol, ethanol, chloroform, 1,4-dioxane and DMF.

In the IR spectra, Schiff bases DBT-I, DBT-II and DBT-III exhibit strong peaks in the region 1610 cm^{-1}, 1604 cm^{-1} and 1611 cm^{-1} respectively, which can be assigned as ν(HC=N) vibration of azomethine group. Aromatic ν(C-H) stretching at 3045-3040 cm^{-1} and ν(C=C) bands at 1510 cm^{-1}, 1505 cm^{-1}, 1511 cm^{-1} proved existence of aromatic rings. The bands ν(C-S-C) region 722-753 cm^{-1}. The band of hydroxy functional group ν(OH) of DBT-II Schiff base observed at 3127 cm^{-1}. The band of N, N-dimethyl functional group ν(N(CH_3)$_2$) of DBT-I Schiff base observed at 2815 cm^{-1}.

The mass spectrum of Schiff bases DBT-I, DBT-II and DBT-III showed the molecular ion peak at m/z 318.1, 368.9 and 335.2 that corresponds to the molecular weight of Schiff base.

In the ^{1}H NMR spectra of benzothiazole Schiff bases, multi signals are assigned to Aromatic protons observed in the range from 6.8 to 7.65 δppm. A sharp singlet is observed for Schiff bases DBT-I, DBT-II and DBT-III at 9.26 δppm, 7.26 δppm and 7.14 δppm respectively in spectrum which corresponds to the azomethine proton. Methyl group protons for DBT-I appears as singlet at 1.63 δppm. The hydroxyl group proton for DBT-II is observed as a broad singlet at 5.72 δppm in the spectrum. In the ^{1}H NMR spectra of

DBT-III, methoxy group protons appear as singlet at 3.98 δ ppm.

3.2. Antimicrobial activity

Synthesized Schiff bases were tested for their impact on some microorganisms in terms of minimum inhibitory concentration (MIC) using suspended Luria Broth in sterile double distilled water as a media. Culture for bacteria gram negative and positive was incubated for 24 hrs at 35°C, respectively. Control test with no active ingredient was also performed by adding just an equivalent amount of solvent. MIC was determined using double fold serial dilution in liquid media containing varying concentration of tested compounds from 0.1–10,000 µM. Bacterial growth was measured by the turbidity of the culture after 15 h. If particular concentration of the compound inhibited bacterial growth, half the concentration of the compound was tried. This procedure was carried out at a concentration that bacteria grow normally.The lowest concentration that inhibits the bacterial growth totally was determined as MIC value. All equipment and culture media employed during the process were sterile.

The efficiencies of the ligands and the complexes have been tested against two Gram-positive (S. aureus, B. subtilis), two Gram-negative (S. marcescens, E. coli) bacteria and two fungus (Rhizopus sp., A. niger). The data reveals that all the synthesized Schiff bases have higher antimicrobial activity.

Among the various compounds, DBT-III has been found to be the most effective against these microbes showing maximum clarity of zones. Its antibacterial activity was found maximum against Gram positive bacteria (S. aureus, B. subtilis) and Gram-negative bacteria (*E. coli*) and DBT-I also exhibited maximum inhibition against S. marcescens, and DBT-II exhibited minimum inhibition.

The growth of fungus was measured by recording diameter of fungal colony. Following relation was used to calculate the fungal growth inhibition:

Fungal growth inhibition (%) = [(A – B)/A] x 100

where A is the diameter of the fungal colony in the control plate and B is the diameter of the fungal colony in the test plate. Results are represented in figure-10. Among all compounds DBT-II, has shown maximum antifungal activity compared to DBT-I, DBT-II against A. niger while DBT-III exhibited maximum anti-fungal activity against Rhizopus sp. The comparison chart against standard antibiotics is as given in Figure-1.

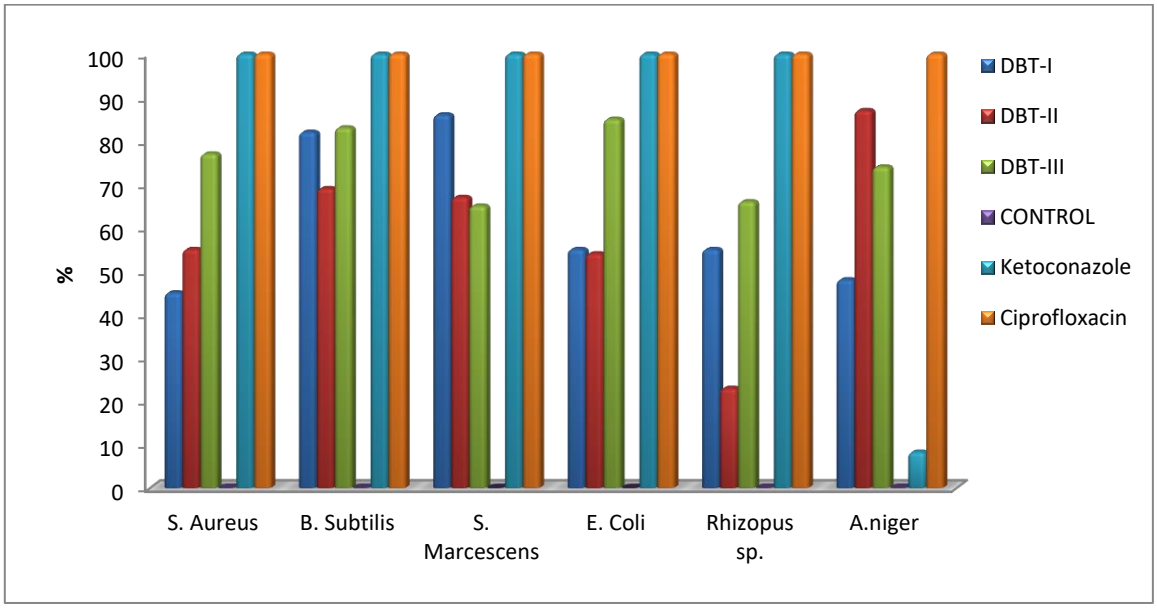


Figure-1: Comparison diagram of antimicrobial activity

CONCLUSION

In this paper, we have described new Schiff bases, synthesized by condensation of 4,6-difluoro-2-amino benzothiazole and different aldehydes like *N, N-dimethyl benzaldehyde, 5-bromo-2-hydroxy benzaldehyde* and *3,4-dimethoxy benzaldehyde* in an alcoholic medium using glaciel acetic acid with good yield. The structure of Schiff bases has been confirmed by various physicochemical and spectral analyses. In this study, these Schiff base derivatives DBT-I, DBT-II and DBT-III are found active antimicrobial compounds. Among the three Schiff

base tested, DBT-III exhibited the promising antimicrobial activity and DBT-II is the most active against A. niger.

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