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Synthesis, Characterization and Biological Screening of Schiff bases derived from 4, 6-difluoro-2-amino Benzothiazole

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Abstract

Novel benzothiazole Schiff bases namely *N-(4-chlorobenzylidene)-4,6-difluorobenzothiazole-2-amine; 4,6-difluoro-N-(4-nitrobenzylidene)benzothiazol-2-amine* and *N-((1H-indol-3-yl)methylene)-4,6-difluorobenzothiazole-2-amine* have been synthesized from condensation reaction of 4,6-difluoro-2-amino benzothiazole with different aromatic aldehydes like *4-chlorobenzaldehyde, 4-nitrobenzaldehyde* and *1H-indole-3-cardaldehyde*. The structures of all the compounds were characterized by elemental analysis, FT-IR, Mass and ^{1}H-NMR spectroscopy. Schiff bases have been screened for antimicrobial activity against bacteria and fungi by using MIC determination. *In vitro* antibacterial and antifungal activity of ligands were assayed against gram positive (*S. Aureus, B.Subtilis*), gram negative bacteria (*S. Marcescens, E. coli*) and *Rhizopus sp.* and *A. Niger*. The standard drugs ketoconazole and ciprofloxacin were used to screen antimicrobial activity.

Keywords: Schiff Base; 4,6-difluoro-2-aminobenzothiazole; Antibacterial Activity; Antifungal Activity; MIC determination

Introduction

Benzothiazole is a heterocyclic and bicyclic ring compound and its bicyclic ring consist of 1,3-thiazole ring fused with benzene ring. Thiazole is a five membered ring containing nitrogen and sulfur heteroatoms. The heterocyclic compounds play a vital role in the metabolism of all the living cells and they are very largely distributed in nature and very essential to living organisms. Among large number of nitrogen heterocycles are the most abundant specially those containing oxygen and Sulphur [1-5]. Benzothiazole moieties are widely found in bioorganic and medicinal chemistry with application in drug discovery. Benzothiazoles with multiple applications which have been attracted considerable attention of medicinal chemists due to their wide range of biological activities which include antitumor [6,7], antimicrobial [8], antibacterial [9,10], antifungal [11], anti-inflammatory [12], anticonvulsive [13], analgesic [14], cytotoxic [15], inhibition of enzyme [16] and Parkinson's disease [17]. Schiff base synthesized from benzothiazole derivatives are of great importance due to their wide applications as antimicrobial, anti-degenerative, anti-inflammatory, anti-HIV agents [18-21] and so forth. Further, some of these schiff bases have other applications as corrosion inhibitor [22], dye manufacture [23], perfumery [24], plant growth regulators [25], Sensor and nanomaterial [1-4,26-28] for various synthesis [29-31]. Specifically, the study of Schiff bases with benzothiazole derivatives is of considerable current interest in recent years due to their biological and pharmaceutical applications.

Compounds containing azomethine group (-HC=N-) are known as Schiff base [32], which are condensation product of primary amines with aldehydes or ketones (R-CH=N-R', where R and R' represents alkyl and/or aryl substituents) and were first reported by Hugo Schiff in 1864 [33]. Schiff bases have been shown to possess/exhibit many biological activities such as anticancer [34], antituberculosis [35],

antibacterial [36], antimicrobial [37], plant growth inhibitors [38] and anti-inflammatory activity [39].

Here in this paper, we have reported synthesis and characterization of novel Schiff bases derived from 4,6-difluoro-2-aminobenzothiazole. All the synthesized compounds were screened for their antibacterial and antifungal activity 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* using MIC determination in solvent DMF/$CHCl_3$.

Experimental

Chemicals and Reagents

All commercially available AR grade chemicals were used as received without further purification. Chemical reagents and solvents were obtained from Sigma-Aldrich. Silica gel and fluorescence active TLC plates (F-2009) were purchased from E.Merck.

Instrumentation

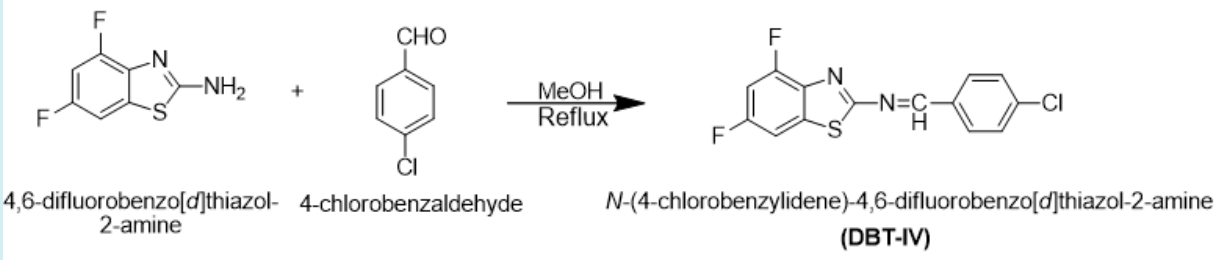
Melting points were determined using capillary and theils tubes filled with paraffin oil and are uncorrected. The Percentage of C, H, N and S were derived using CHN/S/O Analyser, Perkin Elmer, series11, 2400. Elemental analysis data are in accordance with the theoretically calculated percentage of C, H, N and S. FT-IR spectra of the compounds were recorded in the range 4000-400cm^{-1} on tensor Bruker 27 (Ettlingen, Germany) using KBr pellets. Mass spectra (GC-MS) were determined using Jeol D-300 spectrometer. ^{1}H-NMR spectra were recorded on a model DPX 200 MHz and Advance II 500 MHz Bruker FT-NMR instruments (Ettlingen, Germany) using TMS as internal reference.

Preparation of Amine

Amine was synthesized by reported method [40]. To an ethanolic solution of 3, 5-difluoro aniline and potassium thiocyanate was mixed containing 2ml concentrated HCl. To this mixture, bromine in glaciel acetic acid was added and the reaction mixture was refluxed for 1hr. Then, reaction mixture was poured into crushed ice and precipitates obtained with stirring. Precipitate was filtered, washed with cold water and dried. The crude product was recrystalized from ethanol.

Synthesis of Schiff Base

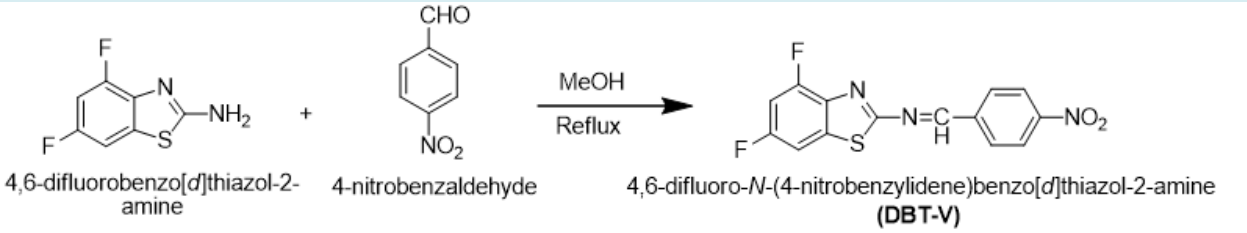
Synthesis of N-(4-chlorobenzylidene)-4,6-difluorobenzothiazole-2-amine: To a solution of 4,6-difluoro-2-amino benzothiazole (0.186gm,0.001mol) and 4-chloro benzaldehyde (0.140gm, 0.001 mol) were dissolved in methanol using catalytic amount of glacial acetic acid. The reaction mixture was refluxed with constant stirring at 50-60°C for 4-5 hrs. Then, progress of reaction checked by TLC. It was cooled at room temperature and product was filtered, dried by ether and recrystallized from hot methanol. To remove excess aldehyde, the product was washed with sodium bisulphite and then washed with chilled methanol to remove other impurities. Yield: 58.58% (Scheme 1).



4,6-difluorobenzo[*d*]thiazol-2-amine | 4-chlorobenzaldehyde | *N*-(4-chlorobenzylidene)-4,6-difluorobenzo[*d*]thiazol-2-amine **(DBT-IV)**

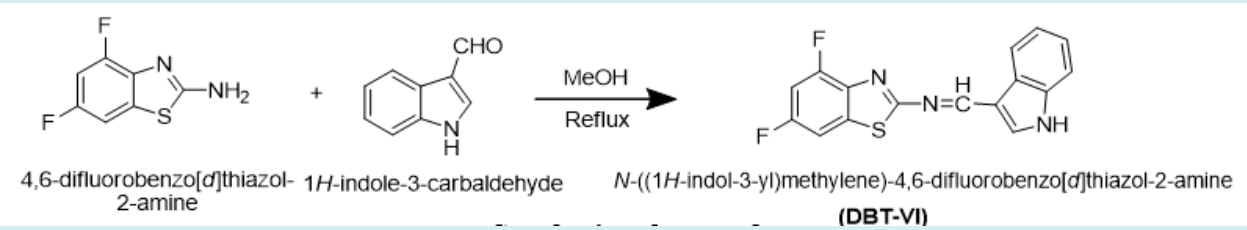
Scheme 1: For $C_{14}H_7ClF_2N_2S$, Melting point is 169-172°C and Elemental analysis data found: %C 54.36; %H 2.31; %N 8.99; %S 9.88. In FT-IR, bands observed are at 1669 cm^{-1} ν(HC=N, azomethine group), 834 cm^{-1} ν(C-Cl), 1218 cm^{-1} ν(C-F), 789 cm^{-1} ν(C-S-C). ^{1}H-NMR (500 MHz, $CDCl_3$): δAr-H, 6.87-7.45 (d, 6H); δN=CH, 8.05 (s, 1H) and Mass spectra (GC-MS) *m/z* values of **DBT-IV** correspond to the M^+ adduct (309.2).

Synthesis of 4,6-difluoro-N-(4-nitrobenzylidene) benzothiazol-2-amine: To a solution of 4,6-difluoro-2-amino benzothiazole (0.186gm,0.001mol) and 4-nitro benzaldehyde (0.151 gm, 0.001 mol) were dissolved in methanol using catalytic amount of glacial acetic acid. The reaction mixture was refluxed with constant stirring at 50-60°C for 4-5 hrs. Then, progress of reaction checked by TLC. It was cooled at room temperature and product was filtered, dried by ether and recrystallized from hot methanol. 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% (Scheme 2). The Schiff base ligand exists in amorphous form and yellow in color.



Scheme 2: For $C_{14}H_7F_2N_3O_2S$, Melting point is 178-180˚C and Elemental analysis data found: %C 52.22; %H 2.24; %N 13.06; %S 9.98. In FT-IR, bands observed are at 1699 cm^{-1} ν(HC=N, azomethine group), 1455 cm^{-1} ν(C-NO2), 1226 cm^{-1} ν(C-F), 760 cm^{-1} ν(C-S-C). ^{1}H-NMR (500 MHz, $CDCl_3$): δAr-H, 6.85-7.77 (d, 6H); δN=CH, 7.26 (s, 1H) and Mass spectra (GC-MS) *m/z* values of DBT-V correspond to the M^+ adduct (320.1).

Synthesis of N-((1H-indol-3-yl)methylene)-4,6-difluorobenzothiazole-2-amine: To a solution of 4,6-difluoro-2-amino benzothiazole (0.186gm,0.001 mol) and 1H-indol-3-carbaldehyde (0.145 gm, 0.001 mol) were dissolved in methanol using catalytic amount of glacial acetic acid. The reaction mixture was refluxed with constant stirring at 50-60˚C for 5-7 hrs. Then, progress of reaction checked by TLC. It was cooled at room temperature and product was filtered, dried by ether and recrystallized from hot methanol. 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% (Scheme 3). The Schiff base ligand exists in crystalline form and pale yellow in color.



Scheme 3: For $C_{16}H_9F_2N_3S$, Melting point is 169-172˚C. Elemental analysis data found: %C 61.11; %H 2.93; %N 13.21; %S 10.07. In FT-IR, bands are observed at 1597 cm^{-1} ν(HC=N, azomethine group), 1215 cm^{-1} ν(C-F), 750 cm^{-1} ν(C-S-C). ^{1}H-NMR (500 MHz, $CDCl_3$): δAr-NH, 10.08 (s, 1H); δAr-H, 6.81-7.26 (d, 7H); δN=CH, 7.86 (s, 1H) and Mass spectra (GC-MS) m/z values of DBT-VI correspond to the M adduct (313.2).

Antimicrobial Activity

The Schiff bases were screened for its antibacterial activity against two Gram positive bacteria *S. Aureus, B. Subtilis* and two Gram negative bacteria *i.e. S. Marcescens, E. Coli* and their antifungal activity against two fungal strains *Rhizopus sp.* and *A. Niger* using MIC Determination in DMF/$CHCl_3$ solvent. Minimum inhibitory concentration (MIC) using suspended Luria Broth in sterile double distilled water as a media. 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 0.1–10,000μM. Bacterial growth was measured by the turbidity of the culture after 15h. 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 prepared discs were placed on the surface of the cultured media with each of bacteria incubated for 24hrs at 37°C. The zone of inhibition were measured against all microorganisms in mm. Ketoconazole and Ciprofloxacin were used as the reference drug. 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 and Discussion

The novel Schiff base compound DBT-IV, DBT-V and DBT-VI are synthesized according to described process in scheme-1,2 and 3 respectively. The structures of all the compounds were confirmed on the basis of elemental analysis, FT-IR, mass and 1H NMR spectral data. The ligands were insoluble in water but soluble in methanol, ethanol, chloroform, 1,4-dioxane and DMF.

FT-IR Spectral Studies

Formation of Schiff base is confirmed by disappearances of carbonyl and amine group peaks and appearance of peak of azomethine group in IR spectrum. FT-IR spectra of Schiff bases were recorded in the 400-4000 cm^{-1} on tensor Bruker 27 (Ettlingen, Germany) using KBr pellets technique. The IR spectrum gives information regarding the nature of functional groups present in the molecule. The spectrum of unknown compound can be interpreted and identified by comparision to library of known compounds. In the IR spectra, Schiff bases showed a strong band in the range 1597-1699cm^{-1}, which corresponds to the azomethine (HC=N) group. Aromatic ν(C-H) stretching at 3045-3040cm^{-1} and ν(C=C) bands at 1519cm^{-1}, 1488cm^{-1}, 1510cm^{-1} proved existence of aromatic rings. In these molecules, the bands of ν(C-S-C) are observed in the region at 750-789 cm^{-1}. A strong band of nitro functional group ν(C-NO_2) of DBT-V Schiff base is observed at 1455 cm^{-1}. The band of chlorine functional group ν(C-Cl) of DBT-IV schiff base observed at 834 cm^{-1}.

Mass Spectral Studies

Schiff bases have been studied for their mass spectral analysis. The mass spectra were measured to confirm the composition and purity of ligands under investigation. The mass spectrum of Schiff bases DBT-IV, DBT-V and DBT-VI exhibit the molecular ion peak at m/z 309.2, 320.1 and 313.2 that corresponds to the molecular weight of Schiff base.

^{1}H NMR Spectral Studies

The data of ^{1}H-NMR spectra of Schiff base were measured in $CDCl_3$ using TMS as an internal reference. In the 1H 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 singlet is observed for Schiff bases DBT-IV, DBT-V and DBT-VI at 8.05 δppm, 7.26 δppm and 7.86 δppm respectively in spectrum which corresponds to the azomethine proton.

Antimicrobial Activity

Synthesized Schiff bases were screened for their antimicrobial activity on the some microorganisms in terms of minimum inhibitory concentration (MIC). The bio-efficiency of the ligands 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-IV has been found to be the most effective against Gram-positive microbes showing maximum clarity of zones. Its antibacterial activity was found maximum against Gram positive bacteria (S. aureus, B. subtilis) and DBT-VI also exhibited maximum inhibition against Gram-negative bacteria S. marcescens and E. Coli. DBT-V exhibited minimum inhibition against all the microorganisms.

Among all compounds DBT-V, has shown maximum antifungal activity compared to DBT-IV, DBT-VI against both the fungal strains Rhizopus sp. and A. Niger while DBT-IV and DBT-VI exhibited moderate antifungal activity against Rhizopus sp. and A. Niger respectively. The comparison chart against standard antibiotics is as given in Figure 1.

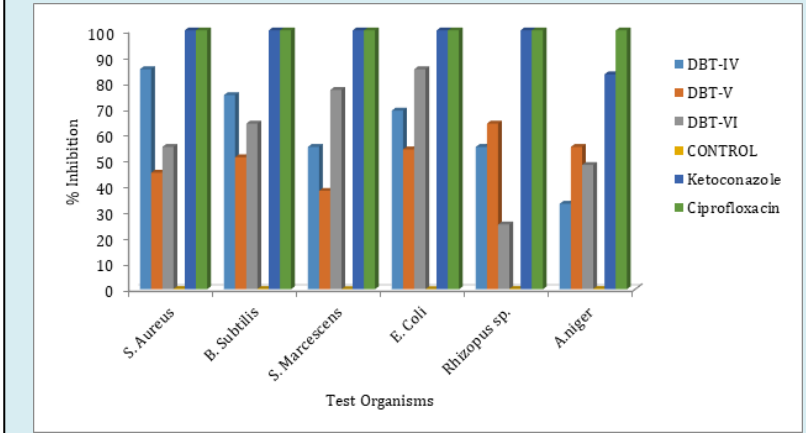


Figure 1: Comparison diagram of antimicrobial activity.

Conclusion

In this paper, Three novel Schiff bases have been synthesized by condensation reaction of 4,6-difluoro-2-amino benzothiazole and different aldehydes like *4-chlorobenzaldehyde*, *4-nitrobenzaldehyde* and *1H-indole-3-cardaldehyde* in an alcoholic medium using glaciel acetic acid give DBT-IV, DBT-V and DBT-VI with good yield. The structure of Schiff bases have been confirmed by various physicochemical and spectral analyses. In this study, these Schiff base derivatives DBT-IV, DBT-V and DBT-VI are found active antimicrobial compounds. Among the three Schiff base tested, DBT-IV and DBT-VI exhibited the promising antimicrobial activity and DBT-V is most active against both the fungal strains.

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