Imino-4-Methoxyphenol Thiazole Derived Schiff Base Ligands: Synthesis, Spectral Characterization and Antimicrobial Activity

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Abstract

Two imino-4-methoxyphenol thiazole derived Schiff bases, 3-(5-nitrothiazol-2-ylimino)methyl)-4-methoxyphenol (4) and 3-(5-ethyl-1,3,4-thiadiazol-2-ylimino)methyl)-4-methoxyphenol (5) were synthesized by condensing 2-amino-5-nitrothiazole (1) and 2-amino-5-ethyl-1,3,4-thiadiazole (2) with 5-hydroxy-2-methoxybenzaldehyde (3). The obtained ligands were characterized by using UV-visible, $^1$H, $^{13}$C-NMR and MS techniques. Data obtained from the above techniques confirmed the molecular structures of the obtained compounds. The optimized structures of the compounds were done using ACD simulation software. The synthesized compounds were tested for their antibacterial (E. coli and R. solanacearum) and antifungal (F. oxysporum and A. niger) activities. The results from these studies showed that the compounds are moderately active against the tested species of bacteria and fungi. The microbial growth inhibition by compound 4 was significantly higher than compound 5. Microbial growth inhibition activity of both the compounds was less compared with their standard drugs.

Keywords: Iminothiazole; Schiff base; NMR; Mass spectroscopy; Antimicrobial activity.

Introduction

Schiff bases will be obtained upon the condensation of primary amines with carbonyl compounds [1,2]. Intramolecular hydrogen bonding between hydroxyl (OH) hydrogen and azomethine (C=N) nitrogen atoms of Schiff bases decides the properties of various molecular systems and plays a significant role in many biochemical mechanisms [3]. Also, C=N linkage in the azomethine derivatives is essential for biological activity [4]. Although there are wide applications of Schiff in biological systems [5], catalysis [6] and analytical applications [7], the spectral studies of the Schiff bases containing a heterocyclic ring are comparatively minor. These Schiff bases are well known to have biological activities such as antimicrobial [8,9], antifungal [10,11], antitumor [12,13] and as herbicides [14]. In particular, thiazole and derivatives have been found number of applications in medicopharmaceutical fields and also some of them were depicted to have antitumor activity [15]. Especially, benzothiazole have shown significant effect against cancer [16]. Hence the Schiff bases derived from thiazole and its compounds are expected to be biologically active. In recent years, the use of antibacterial and antifungal drugs in medicine has increased, especially with the advent of many new diseases across the globe. Efforts have focused on the development of new, less toxic and more efficacious antimicrobial drugs with novel mechanism of action.

The purpose of this study was to synthesize of some thiazole derivatives and to evaluate their activity against some species of bacteria and fungi. In the current research paper, author has reported two Schiff base compounds derived from thiazole backbone, thorough characterization and antimicrobial studies of synthesized compounds against selected species of bacteria and fungi.

Materials and Methods

Chemicals and instruments

All the chemicals and solvents were of AnalAR grade. 5-ethy1-1,3,4-thiadiazol-2-amine was procured from Sigma-Aldrich, Bangalore and used as received. The spectroscopic grade solvents were used as supplied by commercial sources without any further purification. Thin layer chromatography was performed using Silica Gel G (Merck Index) pre-coated plates and the spots were visualized by exposure to UV light. $^1$H and $^{13}$C-NMR spectra were recorded on a BRUKER AVANCE-400 spectrometer. Mass spectra as obtained on Bruker Daltonics 6000 plus mass spectrometer with ESI-MS mode. Antibacterial and antifungal activities of compounds under investigation was determined by Disc diffusion method [17] and Batemann poisoned technique [18], respectively.

General synthesis procedure

Schiff bases 4 and 5 was synthesized by the condensation of 2-amino-5-nitrothiazole (1) and 2-amino-5-ethyl-1,3,4-thiadiazole (2) with 5-hydroxy-2-methoxybenzaldehyde (3) in 1:1 ratio in methanol. The general synthesis route of new Schiff base compounds is depicted in Scheme 1.

Synthesis of 3-(5-nitrothiazol-2-ylimino)methyl)-4-methoxyphenol (4)

To a solution of 2-amino-5-nitrothiazole (10 mmol, 1.49 g) in 20 ml methanol, 5-hydroxy-2-methoxybenzaldehyde (10 mmol, 1.57 g) in methanol (10 ml) was added dropwise with continuous stirring for 10 min and the reaction mixture was then refluxed for 6 h with stirring. Completion of the reaction was monitored time-
for C11H9N3O4S [M + K]+: 318.03; found 318.27.

131.4, 130.5, 130.3, 129.7, 129.3, 128.4, 127.9, 126.2, 50.1. ESI-MS calc.
in vacuum desiccator. Yield: 82%. 1H NMR (DMSO-d6, ppm), δ 10.36
precipitated by pouring into ice cold water, filtered, dried and stored
to-time by TLC. After the completion, the reaction mixture was
by pouring into ice cold water, filtered, dried and stored in vacuum
stirring for 10 min and the reaction mixture was then refluxed for 6 h
1.57 g) in methanol (10 ml) was added dropwise with continuous

Scheme 1: Synthesis of thiazole Schiff base derivatives (4 and 5).

Synthesis of 3-(5-ethyl-1,3,4-thiadiazol-2-ylimino)methyl)-4-
methoxyphenol (5)
To a solution of 2-amino-5-ethyl-1,3,4-thiadiazole (10 mmol, 1.30
g) in 20 ml methanol, 5-hydroxy-2-methoxybenzaldehyde (10 mmol, 1.57 g) in methanol (10 ml) was added dropwise with continuous
stirring for 10 min and the reaction mixture was then refluxed for 6 h
with stirring. Completion of the reaction was monitored time-to-time
by TLC. After the completion, the reaction mixture was precipitated
by pouring into ice cold water, filtered, dried and stored in vacuum
desiccator. Yield: 79%. 1H NMR (DMSO-d6, ppm), δ 8.37 (s, 1H, imine
CH), 7.78 (d, 1H, Ar-H), 7.71 (d, 1H, Ar-H), 3.51 (s, 3H, OCH3); 13C NMR (DMSO-d6, ppm), δ 171.2, 135.8, 131.4, 130.5, 130.3, 129.7, 129.3, 128.4, 127.9, 126.2, 50.1. ESI-MS calc.
for C12H13N3O2S [M + K]+: 318.03; found 318.27.

Antimicrobial Screening

Antibacterial screening by disc diffusion method
Antibacterial activity of test compounds 4 and 5 was determined against E. coli and R. solanacearum. The pure cultures of these organisms were obtained from the Division of Biotechnology, JSS University, Mysore-15. The fungi A. flavus and A. Niger were cultured for seven days on Czapek's agar in sterile petridishes under 12/12 h light and darkness. Colonies were isolated for fungal studies after growing to required diameter. The testing compounds (dissolved in DMSO) were added to 10-15 ml of sterilized media to achieve concentration at 35 ± 3°C allowed the media for solidification. The fungi A. flavus and A. Niger were taken as 2 mm disks from 10 days old pure colonies and placed in the petriplates containing Czapek's agar nutrient medium. The experiments were carried out in four replicates per treatment and incubation was carried out at 22 ± 1°C under 12/12 h light and darkness. The radial growth of the colony was recorded after 96 h of incubation and mean diameter of mycelia growth in each treatment was recorded. The average percentage inhibition was calculated on the growth media compared to controls using the Vincent formula [19].

Results and Discussion
The synthetic route of Schiff base compounds 4 and 5 is represented in Scheme 1. The reported compounds were synthesized by following literature procedures [20]. The compounds have been characterized by NMR (1H and 13C), MS and UV-Vis spectroscopic techniques.

The representative NMR (1H and 13C) spectra of compound 4 are shown in Figure 1. The 1H NMR spectra of the compounds provide useful information about the imine CH protons which exhibited resonance in the region δ 8.25-8.43 (Figure 1a and 1b). A broad singlet at δ 10.36 in the proton NMR spectrum of 4 is observed due to the -OH group. Mass spectrum of compound 4 is shown in Figure 2. The detailed data obtained for 1H, 13C and MS of the reported compounds are provided in the experimental section.

The UV-Vis absorption spectra of the compounds 4 and 5 are recorded in ethanol at ambient temperature. As shown in Figure 3, the UV-Vis spectra of 4 and 5 exhibits four bands each and out of which two bands are encountered towards higher energy in the region 219-246 and 221-252 nm, respectively. These bands are due to transition of π electrons in the aromatic rings. (π–π* transition). The third and fourth bands in both the compounds appears more or less in the same region around 275-347 nm due to π–π* transition with in the imine group and 362-459 nm due to an intramolecular charge transfer interactions within the whole molecule [21].

Antimicrobial Activity
The biological results obtained are presented in the Table 1. In this study, the concentration of the test compounds and standard drugs were at 400 ppm in DMSO. The test compounds 4 and 5 showed less inhibition of the bacterial growth in comparison with standard drug Chloramphenicol. Both the compounds showed same inhibition potential against E. coli but compound 4 showed high inhibition effect than compound 5 against R. solanacearum (Supplementary Figures). The reason for this increased inhibition effect may be due to the presence of electron withdrawing nitro group in compound 4.
Similar situation was noticed in antifungal studies. The standard antifungal drug, fluconazole was found more potent than the tested compounds. Here also compound 4 was found more potent than compound 5 against the selected species of fungi. The most probable reason for the inhibition would be the interaction of tested compounds with the membrane proteins of the microbes which will cause the rupture of membrane due to alter in the protein structure and thus growth inhibition [23].

**Conclusion**

We describe the synthesis of 3-(5-nitrothiazol-2-ylimino)methyl)-4-methoxyphenol (4) and 3-(5-ethyl-1,3,4-thiadiazol-2-ylimino)methyl)-4-methoxyphenol (5). The synthesized compounds were characterized using various spectral techniques. The antimicrobial activity of the two methoxyimio thiazole derived Schiff bases, 4 and 5 were tested against selected species of bacterial (E. coli and R. solanacearum) and fungi (F. oxysporum and A. niger). Both the compounds were moderately potent towards the microbial growth inhibition. Particularly, compound 4 was significantly active against the tested microbes than compound 5. The possible reason for this potency of compound 4 may be due to the presence of electron withdrawing nitro group which can alter the tertiary structure of membrane proteins and thus growth. The simulated structures of the compounds are depicted in Figure 4 which was done by using ACD molecular simulation package software.

**Conflict of Interest**

Authors declare that there is no conflict of interest regarding publication of this research work.
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