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Synthesis and characterization of thiadiazole containing Schiff base: Antimicrobial activity

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ABSTRACT

A reaction of primary amine, 5-ethyl-1,3,4-thiadiazol-2-amine ***(1)*** *with substituted aldehydes afforded a new class of imine group containing compounds* ***(3, 5 and 7)****. The synthesized compounds were characterized by using spectroscopic techniques viz., ^{1}H-NMR, ^{13}C-NMR and mass spectral studies. Antimicrobial activity was done using disc diffusion technique using Bacillus subtilis, Escherichia coli, Staphylococcus aureus and Ralsotonia solanacearum and antifungal activity against Aspergillus niger, Aspergillus flavus and Alternaria solani. All the synthesized compounds exhibited potent antimicrobial activities.*

Keywords: Schiff base, spectroscopic studies and antimicrobial activity.

INTRODUCTION

Heterocyclic moieties can be found in a large number of compounds which display biological activity. The biological activity of the compounds is mainly dependent on their molecular structures[**1**]. Over the past decade, the synthesis of privileged classes of heterocyclic molecules has become one of the prime areas of research in synthetic organic chemistry[**2**]. These privileged structures have gained much attention, owing to their potential role as ligands, which are capable of binding multiple biological targets[**3**].

Schiff bases are important class of compounds due to their flexibility, structural similarities with natural biological substances and also due to presence of imine (-N=CH-) which imports in elucidating the mechanism of transformation and rasemination reaction in biological system[**4**]. These novel compounds could also act as valuable ligands whose biological activity has been shown to increase on complexation[**5**].

Among the nitrogen-containing privileged class of molecules, substituted thiadiazole derivatives were considered as important therapeutic scaffolds[**6,7**]. Therefore, in the present investigation, the author has made an effort to synthesize Schiff base ligands of the cited derivatives and also characterized by employing IR, ^{1}H-NMR and mass spectral studies.

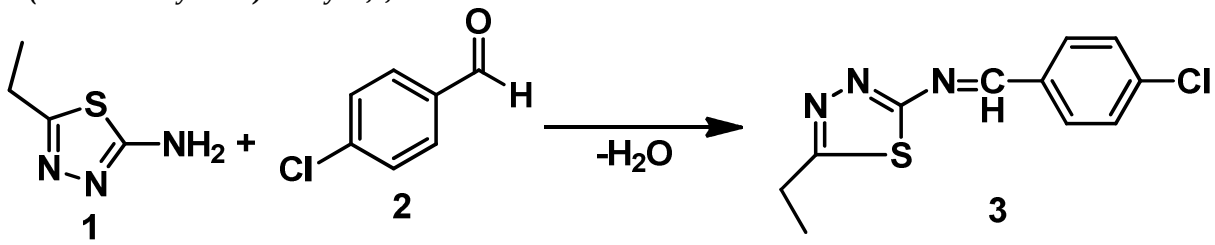
MATERIALS AND METHODS

All the chemicals and solvents were of AnalaR grade. 5-ethyl-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 iodine. All melting points (m.p.) were determined with a Büchi 530 melting point apparatus in open capillaries and are uncorrected. Infrared spectra were recorded in the range 4000-200 cm^{-1} on a JASCO FTIR-8400 spectrophotometer using Nujol mulls between polyethylene sheets. ^{1}H-NMR spectra were obtained on a Varian AC 400 spectrometer. ESI-MS were determined on Varian 1200L model mass spectrometer.

PROCEDURES

Synthesis:

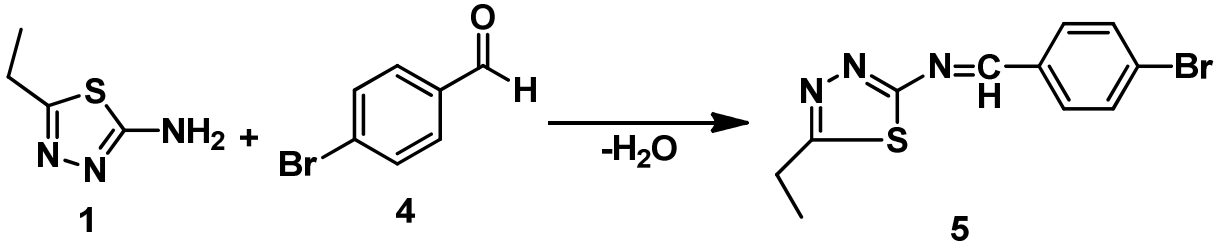
N-(4-chlorobenzylidene)-5-ethyl-1,3,4-thiadiazol-2-amine



A volume of 25 mL methanolic solution of 5-ethyl-1,3,4-thiadiazol-2-amine **(1)** (1.38 g, 10 mmol) was slowly added to a 15 mL of 4-chlorobenzaldehyde **(2)** (1.12 g, 10 mmol in methanol). The reaction mixture was stirred for 30 min and then refluxed for 4h. The completion of reaction was monitored by TLC. The solvent was removed by distillation. The solid product obtained was recrystallized from ethanol to yield final product **(3)**.

Yield : 61%; mp: 174 °C; FT-IR (nujol, ν/cm^{-1}): 3079, 2988, 2353 (C-H), 1655 (C=N), ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.18 (s, CH_3, 3H), 4.21 (dd, CH_2, 2H), 8.14 (s, CH, 1H, -N=CH-), 7.56-7.05 (m, Ar-H, 7H, Aromatic protons); Mass(m/z): 251 [M^+, 81 %].

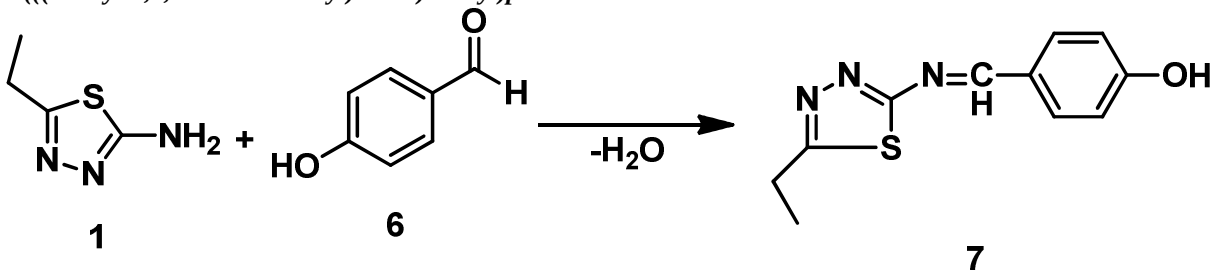
N-(4-bromobenzylidene)-5-ethyl-1,3,4-thiadiazol-2-amine



In a round bottom (RB) flask, a mixture of 5-ethyl-1,3,4-thiadiazol-2-amine **(1)** (1.38 g, 10 mmol in 25 mL methanol) and 4-bromobenzaldehyde **(4)** (1.01 g, 10 mmol in 15 mL methanol) was heated under reflux for 4h with initial stirring of 30 min. The product obtained was concentrated under vacuum, filtered off and recrystallized from ethanol to give final product **(5)**.

Yield : 65 %; mp: 185°C; FT-IR (nujol, ν/cm^{-1}): 3074, 2928, 2157 (Ar-C-H), 1614 (C=N); ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.76 (s, OCH_3, 3H), 4.21 (dd, CH_2, 2H), 8.05 (s, CH, 1H, -N=CH-), 7.48-7.73 (m, Ar-H, 8H, Aromatic protons); Mass(m/z): 295 [M^+, 81 %].

4-(((5-ethyl-1,3,4-thiadiazol-2-yl)imino)methyl)phenol



An equimolar quantities of methanolic solution of both 5-ethyl-1,3,4-thiadiazol-2-amine **(1)** (1.38 g, 10 mmol in 25 mL methanol) and 4-hydroxybenzaldehyde (1.24 g,15 mL of 10 mmol) was stirred for 30 min and refluxed for 4h. The solvent was removed under vacuum and the solid product obtained was filtered, dried and crystallized from ethanol.

Yield : 67%; mp: 212 °C; FT-IR (nujol, ν/cm^{-1}): 3069, 2984, 2906 (Ar-C-H), 1593 (C=N), 3458 (O-H); ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.76 (s, OCH_3, 3H), 4.15 (dd, CH_2, 2H), 8.72 (s, CH, 1H, -N=CH-), 10.12 (s, OH, 1H), 7.48-7.12 (m, Ar-H, 7H, Aromatic protons); Mass(m/z): 233 [M$^+$, 76 %].

Antimicrobial activity

The *in vitro* antimicrobial screening effects of the synthesized compounds were evaluated against four bacteria namely *Bacillus Subtilis*, *Escherichia coli*, *Staphylococcus aureus* and *Ralstonia solanacearum* and three fungi namely *Aspergillus niger*, *Aspergillus flavus* and *Alternaria solani* by disc diffusion method using nutrient agar medium for antibacterial studies and potato dextrose agar medium for antifungal studies[9-12].

RESULTS AND DISCUSSION

The Schiff base ligands were synthesized by the condensation of 5-ethyl-1,3,4-thiadiazol-2-amine with different aromatic aldehydes in 1:1 molar proportion in methanol. The Schiff bases were soluble in methanol, ethanol, DMSO, acetone and insoluble in water. The compounds were purified by repeated recrystallization from ethanol and then dried. The structures of the Schiff bases are confirmed by physical and spectral data and are given below (Figure 1).

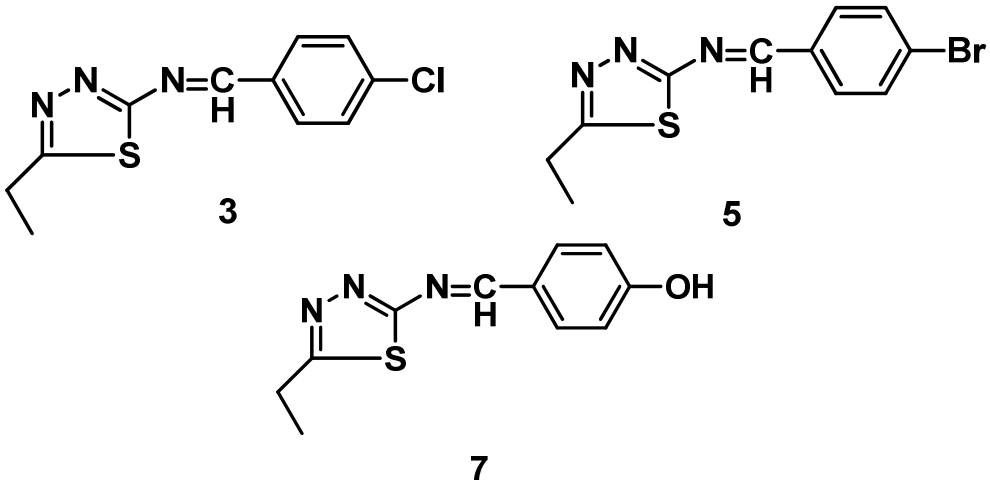


Figure 1. Structures of Schiff base ligands

IR spectra

The IR spectra of the ligands under investigation were recorded by nujol method on JASCO FT-IR spectrophotometer in the frequency range of 4000-400 cm^{-1}. The important diagnostic bands in the IR spectra were assigned and the bands positions are compiled in the synthesis part. IR spectrum of compound 7 is shown as representative spectrum in figure 2.

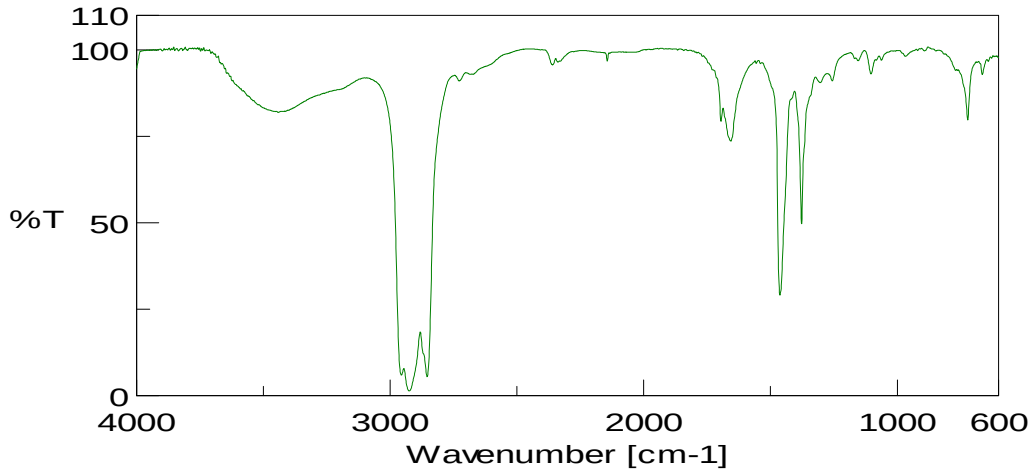


Figure 2. IR spectrum of compound 7

^{1}H-NMR spectra

A review of the literature revealed that NMR spectroscopy has been proven to be useful in establishing the nature and structure of many Schiff bases, as well as their metal complexes in solution. The NMR spectra of Schiff bases were recorded in d_6-dimethylsulfoxide (DMSO) solution, using tetramethylsilane (TMS) as an internal standard on VARIAN-400 NMR spectrometer. Chemical shifts were reported as δ-values in parts per million (ppm) relative to $Si(CH_3)_4$ as relative reference (δ = 0 ppm) and to the solvent as internal reference**.**

Mass Spectra

The mass spectrum was recorded on electron spray ionization (ESI) mode on VARIAN-1200 L model spectrometer. The mass spectra of ligands are compiled in synthetic part.

Antimicrobial results

In the present study, the antimicrobial activity of the Schiff base ligands were evaluated against two Gram-positive (*E.coli and R.solanacearum*), two Gram-negative bacteria (*B.subtilis and S.aureus*) and three fungi (*A. niger, A.flavus and A. solani*). Standard antibiotics namely Chloramphenicol and standard antifungal drug Fluconazole were used for comparison with antibacterial and antifungal activities shown by compounds (Table 1). All the ligands possessed good antibacterial activity against Gram positive bacteria (*E.coli and R.solanacearum*) and antifungal activity against *A. niger* and *A. solani*. However, the ligands exerted moderate to poor activity against *B.subtilis*, *S.aureus* and *A. flavus*. Keeping in view, the rising problems of antimicrobial resistance, these chemical compounds may be used for formulating as novel chemotherapeutic agents.

Table 1: Antimicrobial activity of Schiff base ligands

Compounds	Zone of inhibition (in mm)*						
	Antibacterial activity				Antifungal activity		
	B.subtilis	***E.coli***	***S.aureus***	***R.solanacearum***	***A.niger***	***A. flavus***	***A.solani***
3	13	13	14	09	08	04	08
5	10	12	10	14	10	11	05
7	22	21	22	23	21	13	19
Chloramphenicol	29	26	25	32	-	-	-
Fluconazole	-	-	-	-	27	23	25

**average of three replicates*

CONCLUSION

The work has approached towards the synthetic and biological activities of these wonder molecules, thiadiazol imino derivatives. The preparation procedure follow in this work for the synthesis of title compounds offers reduction in the reaction time, operation simplicity, cleaner reaction and easy work-up. All these Schiff base ligands are insoluble in water but soluble in organic solvents, DMF, DMSO, CH_3Cl and THF. FT-IR and ^{1}H-NMR

spectroscopy confirms the functional groups, particularly -HC=N and O-H groups, of the compounds. All spectroscopic analysis confirmed the proposed structures for these compounds. Antibacterial data have shown that the synthesized compounds have a significant biological activity against the tested microorganisms.

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