SYNTHESES, CHARACTERIZATION AND ANTI BACTERIAL ACTIVITY OF COBALT SCHIFF BASE COMPLEXES CONTAINING THIAZOLE MOIETY

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Abstract- Schiff bases are the condensation products of primary amines with aldehydes or ketones in which the carbonyl group is replaced by imine or azomethine. They are valuable class of organic compounds and able to coordinate a number of different metal ions, hence stabilizing them in a variety of oxidation states. The chemistry of transition metal complexes with Schiff bases is quite rich in terms of applicability. The importance of polydentate Schiff bases cannot be ignored because they can easily be attached to a metal ion due to the formation of highly stable chelates, which are necessary for their action under certain tough conditions. The chemistry of Schiff's bases has attracted chemists for having active role in biological field and a wide range of biological applications such as antiviral, anticancer, anti-bacterial, antifungal, antioxidant, analgesic and antiglycation properties. Moreover, a variety of Schiff bases can inhibit the enzymatic actions due to their structural compatibility to biological systems. The compound containing thiazole moiety show excellent biological activities. Thiazide derivatives of natural or synthetic origin have been applied as antibacterial, antifungal, anticancer and antiviral agents. Keeping in view the above mentioned applications, in the current study Schiff bases 1 and its complex 2 was synthesize and structurally characterize by commonly used spectroscopic technique (NMR). The antibacterial activity of the synthesized compounds has been determined.

Index Terms- Cobalt Schiff base complexes, Synthesis, Characterization, Thiazole ligands, Metal-organic complexes

I. INTRODUCTION

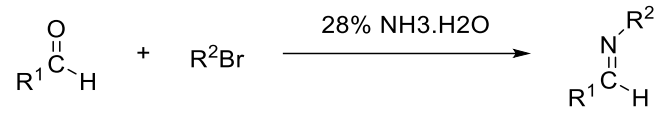
Schiff bases are considered as privileged ligands as they are simply synthesized by condensation of primary amines and carbonyl compounds, aldehydes or ketones. Schiff bases are named for Hugo Schiff, a German chemist, Nobel Prize winner, who discovered them in 1864 [1-2]. Because of their ability to form complexes with transition metal ions, Schiff bases are considered as a very important class of organic compounds. Schiff base ligands are easily synthesized and form complexes with almost all metal ions and coordinating to metal ions via azomethine nitrogen [3]. In coordination chemistry Schiff base ligands have been extensively studied mainly because of their simple syntheses, availability and electronic properties. Recently due to significant roles in analytical chemistry, organic synthesis, refining of metals, electroplating, metallurgy, and photography, Schiff base coordination chemistry has attracted much attention [3]. Schiff bases play vital roles in modern coordination chemistry as well as in the improvement of bioinorganic chemistry. Due to their pharmacological properties they show broad applications in medicine. The C=N in azomethine derivatives is essential for biological activity. Hence, several azomethines were reported to possess antibacterial, antifungal, anticancer and antiviral activities [4-6]. There are also wide applications of Schiff bases in food and dye industry, analytical chemistry, catalysis, fungicidal and agrochemical activities [7-9]. Compounds containing thiazole has been found to be of biological significance, for example vitamin B1 and the coenzyme carboxylase contain a thiazole ring [10]. It is known that 2-aminothiazole is a biologically active compound with a broad range of activity and also is an intermediate in the synthesis of antibiotics and dyes. The penicillin molecule also contains a thiazolidine ring. Metal complexes of thiozole ligands have also attracted considerable attention because of their interesting physico-chemical properties, pronounced biological activities [11-12]. In addition, thiazole containing compounds have significant antitubercular, antibacterial, fungicidal, hypotensive and hypothermic activities [13]. In light of the above-mentioned facts, it is planned to design Schiff bases ligands containing thiozole moiety and their cobalt complexes. These ligands and their cobalt complexes will be characterization and tested for their potentials as antibacterial agents.

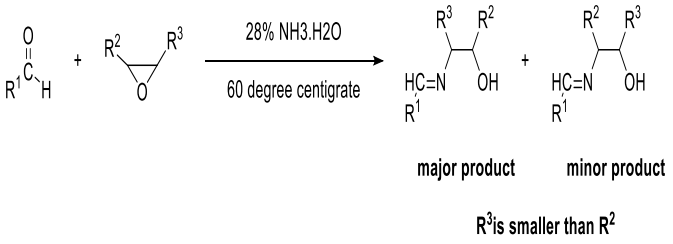
Methods of synthesis of Schiff bases

In the already published literature, Schiff bases have been prepared by different methods, some of them as follows.

Synthesis of Schiff bases using aldehyde and alkyl bromide/epoxide

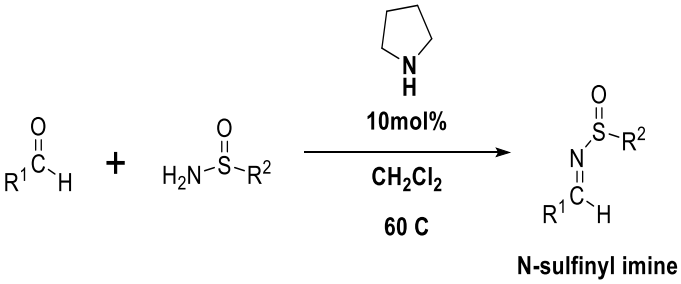
Schiff base can be prepared by the reaction of an aldehyde with alkyl bromide or epoxide in the presence of aqueous ammonia. Aqueous ammonia is used as a nitrogen source as well as a solvent in this reaction. The product yield is excellent for aromatic aldehyde. The Schiff base was obtained from epoxide containing vicinal hydroxide group. [14]

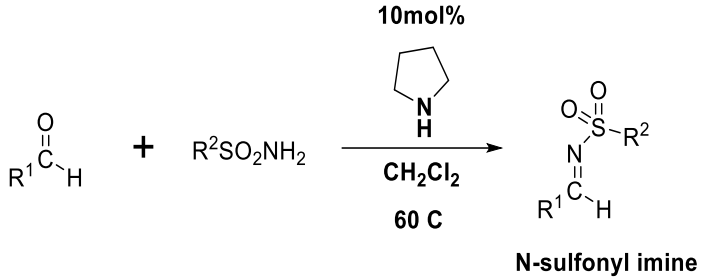


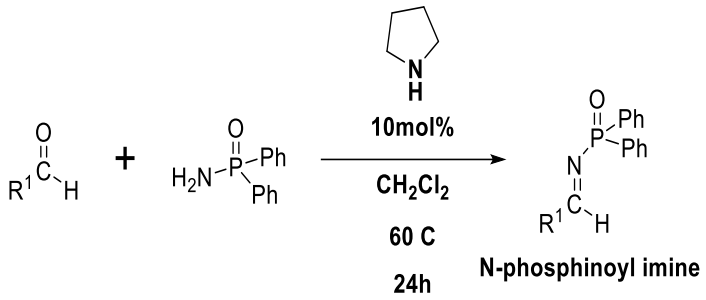


Synthesis of Schiff base from aldehyde in the presence of pyrrolidine catalyst

In this method, the Schiff base has been prepared by the reaction of an aldehyde with a compound bearing an NH2 group in the presence of an organocatalyst called pyrrolidine and CH3Cl2 as a solvent. Under simple conditions and with a little manipulation, this reaction proceeds with a high yield in the absence of acid and metal. This method has been mostly used for the synthesis of N-sulfonyl, N-sulfonyl imines, N-phosphinoyl imines, N-alkyl, and N-aryl imines [15].

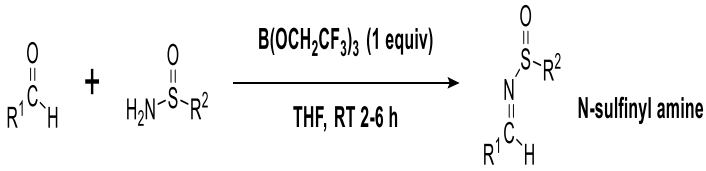


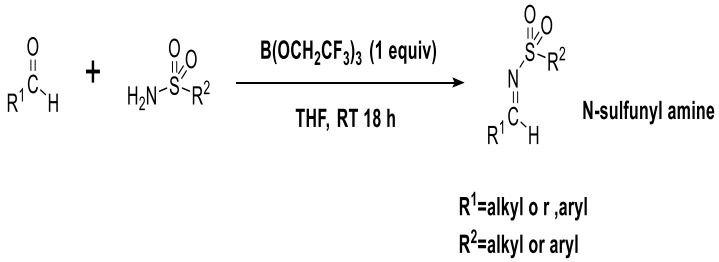


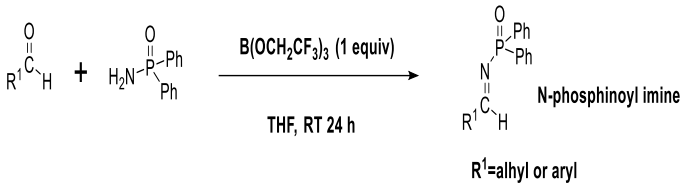


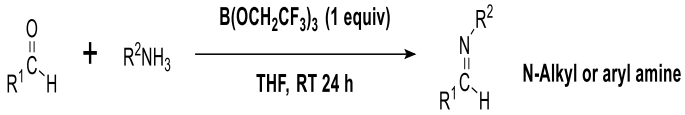
Synthesis of Schiff bases(imines) from aldehyde using Tris(2,2,2-trifluoroethyl) borate

In this method, a variety of Schiff bases (imine) has been prepared by the reaction of an aldehyde with a primary amine in the presence of Tris(2,2,2-trifluoroethyl) borate. At room temperature and by using these reagent imines such as N-Sulfonyl, N-toluene sulfonyl, N- (dimethyl amino) sulfonyl, N-diphenylphosphinoyl, N-(α-methyl benzyl), and N-(4-methoxyphenyl) can easily be synthesized [16]





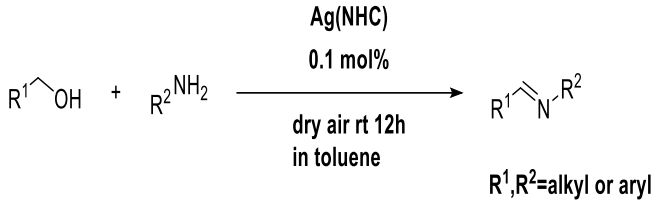


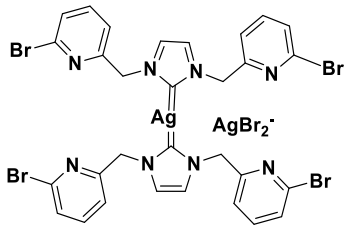


R^1=-alkyl or aryl
R^2=alkyl or aryl

Synthesis of Schiff bases(imines) from alcohol using silver NHC catalyst

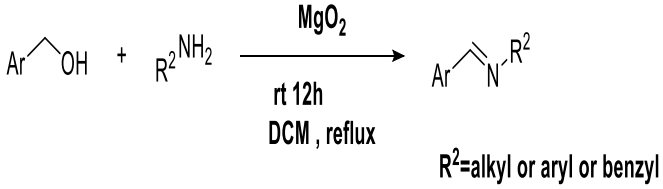
One-pot synthesis of Schiff bases(imines)can be done when alcohol reacts with a primary amine in the presence of a silver NHC catalyst. Only 0.1 mole percent of this catalyst has been used and the yield of this reaction is excellent [17]





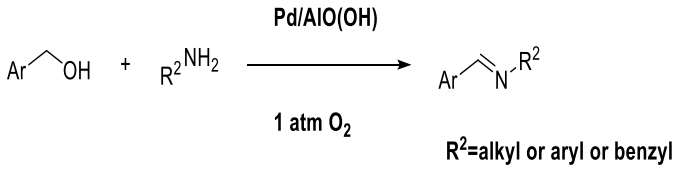
Synthesis of Schiff bases (imines) from alcohol using magnesium oxide as oxidant

One-pot synthesis of Schiff base from the reaction of alcohol with a primary amine in the presence of magnesium oxide as in situ oxidant and DCM as a solvent [18].



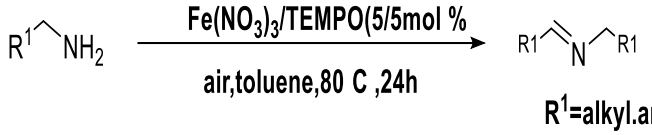
Synthesis of Schiff bases (imines) from alcohol using pd-catalyst

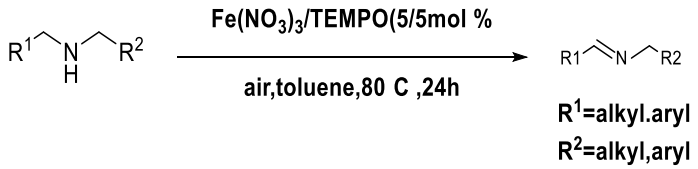
Schiff bases (imines) can be prepared selectively from the reaction of alcohol with a primary amine in the presence of Pd- catalyst under aerobic conditions [19].

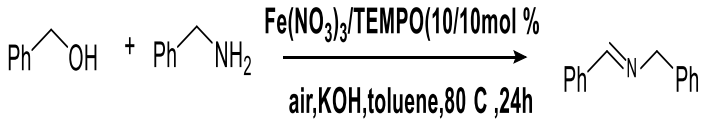


Synthesis of Schiff bases from alcohol and amines in the presence of Fe catalyst under aerobic condition

Schiff bases (imines) can be prepared from the reaction of primary, secondary, benzyl amine with aniline (cross amine reaction) and alcohol with primary amines under oxygen as a safe and greener oxidant and Fe as a catalyst and toluene as a solvent [20].

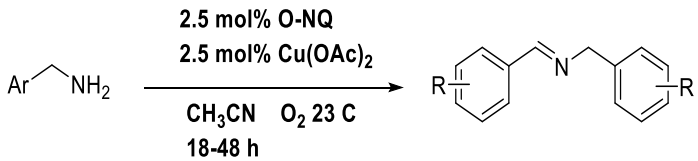


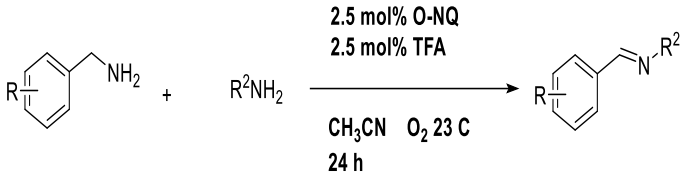




Synthesis of Schiff bases (imines) from primary amines using ortho-naphthoquinone

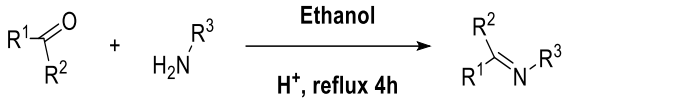
Schiff bases can be prepared from the aerobic oxidation of amine using o-naphthoquinone as a catalyst. O - naphthoquinone along with Cu(OAc)2 permits homocoupling amine reaction while along with TFA causes cross-coupling amine reaction [21]





Synthesis of Schiff bases from the condensation of ketone and a primary amine

Schiff base can be prepared from the condensation reaction of a ketone with a primary amine in an ethanol solvent under acidic conditions. The reaction mixture is allowed to reflux for 4 hours. The reactivity of ketones towards primary amine is relatively less than aldehyde [22].



R^1,R^2 or R^3= alkyl or aryl

Biological applications of Schiff bases

Anti-malarial applications of Schiff bases

Malaria is a neglected disease but still, it causes serious human health problems. According WHO statistical data, every year approximately 500 million people are affected, among them 1-3 million die, while in sub-Sahara Africa maximum percentage are children [23] Malaria is currently found in more than 100 countries throughout Africa, Latin America, Asia, and Oceania. Human malaria is caused by four species of plasmodium (P.falciparum, P.vivax, P.ovale, P.malariae) The female mosquito of the Anopheles genus is responsible for plasmodium [24]. Schiff bases have been shown to be interesting moieties for the design of anti-malarial agents. Ancistrocaldidine is a secondary metabolite produced by plants from families Ancistrocladaceae and Dioncophyllaceae that present an imine group in its molecular scaffold. Compound 1 has been shown to be active against P. falciparum K1 and 3D7. The minimum inhibitory concentrations (MIC values) of ancistrocladidine necessary to completely abolish P. falciparum K1 and 3D7 growth were 0.3 and 1.9 lg/mL, respectively. Interestingly, compound was 90- and 10-fold more selective to P. falcipa- rum K1 and 3D7, respectively than to rat skeletal myoblast L-6cells [25].

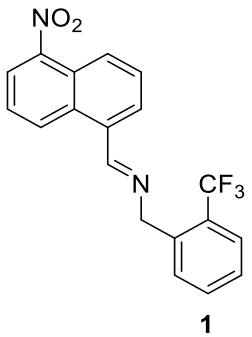


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Figure 1 *Schiff base acting as antioxidant and antimalarial agents*

Antibacterial activity

Schiff bases have been pointed to as promising antibacterial agents. For example, N- (salicylidene)-2-hydroxyaniline is effective against Mycobacterium tuberculosis H37Rv, exhibiting an MIC valve of 81g/ml [26]. The synthesis and antimicrobial activity of a series of Schiff bases derived from the condensation of 5-chloro-salicylaldehyde and primary amines has recently been reported [27]. The 5-chloro-salicylaldehyde-Shiff base derivatives 2-11 (Fig. 2) were most active against at least one of the evaluated bacterial species. Pseudomonas fluorescence was the strain most sensitive to compounds 2-7 and 8-10, with MIC values ranging from 2.5 to 5.2 lg/mL. The MIC value for the reference drug kanamycin against the same bacterial strain was 3.9 lg/mL. The Schiff bases 2, 4-6, 9, and 11 presented MIC values in the range of 1.6–5.7 lg/mL against Escherichia coli, while the MIC value for kanamycin was 3.9 lg/mL. Bacillus subtilis was sensitive to the Schiff base 9 only (MIC = 1.8 lg/mL). The MIC values for compounds 2 and 3 against Staphylococcus aureus were, respectively, 3.1 and 1.6 lg/mL [28].

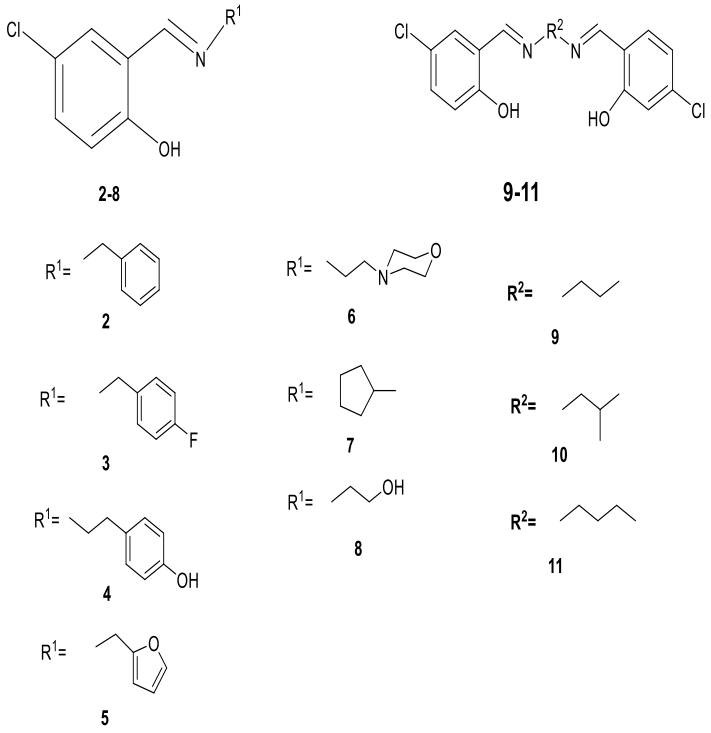
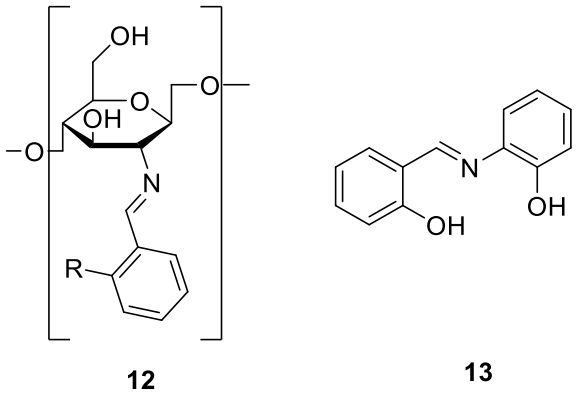


Figure 2 *Chemical structure of some synthetic antibacterial Schiff bases*

Antifungal activity

Some Schiff bases are known to be a good promising actor against fungus. For example, Alternaria brassicae and Alternaria brassicicola are phyto- pathogenic fungi that severely affect the production of most cruciferous crops (broccoli, cauliflower, mustard, turnip, cabbage, rape, and radish) N-(Salicylidene)-2-hydroxyaniline at the concentration of 500 ppm inhibited the growth of these fungi by 67–68% [29]. Compound 12 and 13 are examples of chitosan-derived Schiff bases with antifungal activity. They inhibited the

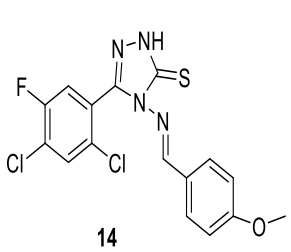
growth of Botrytis cinerea and Colletotrichum lagenarium by 26–33% and 35–38% when used at 1000 ppm, respectively [30].



12 13

Figure 3 *Isatin-derived Schiff bases acting as antifungal agents*

Schiff bases with a 2,4-dichloro-5-fluorophenyl moiety, such as compound 14-18 have been demonstrated to inhibit the growth of fungi of clinical interest, such as Aspergillus fumigatus, Aspergillus flavus, Trichophyton ment-agrophytes, and Penicillium marneffei. The MIC values for these compounds were in the range of 6.3–12.5 lg/mL, indicating that they are as potent as the reference fluconazole [31].



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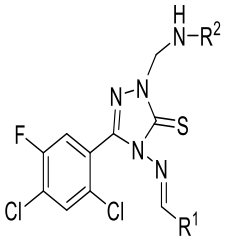


15-18

R^1= 4-F-C_6H_4 and R^2=4-Cl-C_6H_4 15

R^1= 3-Cl-4-F-C_6H_4 and R^2=4-Cl-C_6H_4 16

R^1= 4-F-C_6H_4 and R^2=piperonyl 17

R^1= 3-Cl-4-F-C_6H_4 and R^2=piperonyl18

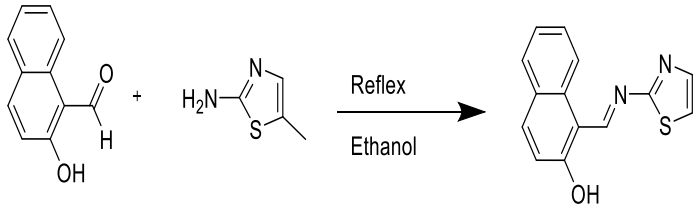
II. METHODOLOGY

Chemicals

All chemicals and other reagents used in this study for the syntheses of ligands and their respective complexes were of analytical grade and used without further purification. Chemicals used during the course of this study are enlisted as below; 2-hydroxy-1-nepthaldehyde, 2-amino thiazole, Glacial acetic acid, Cobalt(II) chloride, Commercial Ethanol, Methanol, Ethyl acetate, Acetonitrile, n-Hexane, Toluene, Acetone, Dichloromethane, Diethyl ether, Benzene, and Chloroform These chemical were obtained from commercial source Sigma Aldrich and were used as received.

Synthesis of (E)-1-((thiazol-2-ylimino) methyl) naphthalen-2-ol 1

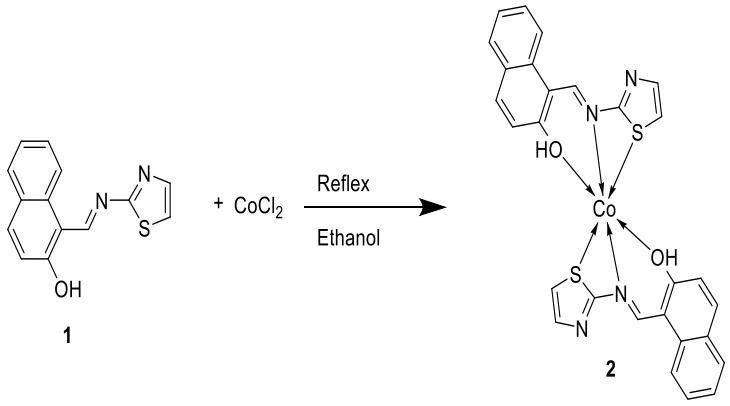
As shown in Scheme 2.1 below, the compound (1) was prepared according to the general procedure as reported in literature [20]. A round bottom flask was charged with ethanolic solution of 2-hydroxy-1-nepthaldehyde (0.5g, 2.9mmol) and few drops of glacial acetic acid. The solution was vigorously stirred and ethanolic solution of 2-amino thiazole (0.3 g,2.9mmol) was added in slight excess. The reaction mixture was heated to reflux for 7 hours. The desired product was obtained as yellow precipitates. The reaction mixture was filtered and the crude products were purified by recrystallization using the same solvent as discussed. The resultant compound was structurally characterized with the help of HNMR.



Scheme 1 *Synthesis of (E)-1-((thiazol-2-ylimino)methyl)naphthalen-2-ol 1*

Synthesis of Cobalt(II) complexes, 2

The complex 2 was prepared by treating Co(II) chloride (0.1 g, 1.50mmol) was taken in a 250mL round bottom flask containing 60mL ethanol, the ligand 1 (0.40g, 3mmol) was added, keeping in view metal-to-ligand ratio as 1:2. The reaction mixture was reflexed for 7 hours. The brownish solid residue was obtained, all volatiles materials and solvent were evaporated under reduced pressure with the help of rotary evaporator and the crude solid was washed with ethanol and dried in open air.



1 2

Scheme 2 *Synthesis Cobalt(II) complex, 2*

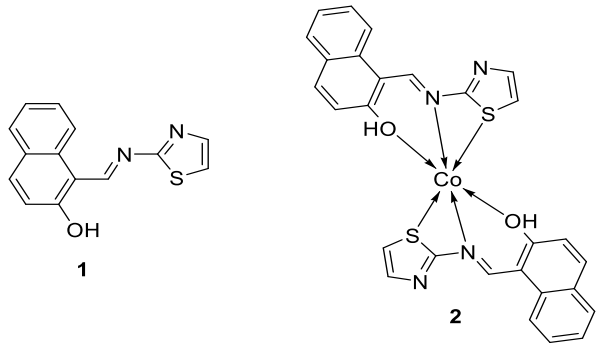
Antibacterial screening of compounds 1,2

The antibacterial potentials of compound 1,2 were determined by a well-known, agar-well diffusion method. Properly washed and dried peltry dishes were used throughout the experiments. Bacterial culture was evenly applied on the surface of the agar peltry dishes. Five wells each of 6 mm diameter were bored in each plate. Afterwards 6.25 mg/mL of each test compound was applied to each well. An available standard antibiotic, Cephradine was used to compare the possible antimicrobial potency of the compound under consideration. All the plates were properly covered and were incubated at 37˚C for 24 hours. The zones of inhibition were measured manually and the said activity of each compound and the standard was expressed in millimeter.

III. RESULTS AND DISCUSSION

Synthesis of (E)-1-((thiazol-2-ylimino) methyl) naphthalen-2-ol 1 and analogous derivative, 2

Proposed structures of compound 1 and 2 are given in Scheme 3.1, below. These compounds were obtained by adopting the literature procedure as discussed in experimental section above. Structures of these compounds were deduced from consistent set of NMR data.



Scheme 3 *Proposed structures of compound 1 and its Zn complex 2*

The ^{1}H NMR spectra of compound 1 exhibit aromatic protons belong to thiazolyl and naphthyl moieties in the range of 8.61 – 6.07 ppm. The appearance of a singlet signal corresponding to N=CH proton at 9.85 ppm show the formation of the expected compound. The proton related OH group is typically broad and appears at 13.85 ppm.

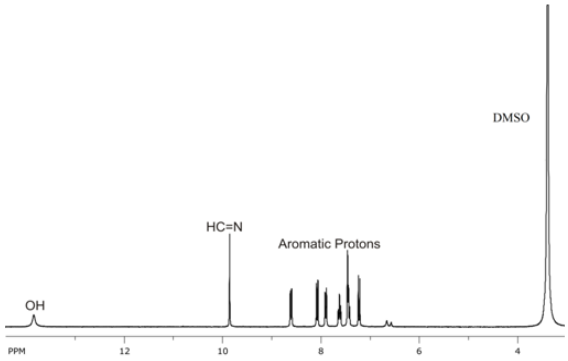


Figure 4 *1H-NMR spectrum of compound 1 measured in DMSO*

Antibacterial activity of compound (1,2)

Antibacterial activities of compounds 1 and 2 were tested in vitro against 4 human pathogenic bacteria Staphylococcus aureus, Escherichia coli, Klebsiella pneumonia and Proteus mirabilis. The activity of these compounds was compared with Ceftriaxone as standard available in the market. Results obtained are summarized in Table 1. It was observed that these compounds show moderate activities against bacteria in comparison with the standard compound. The inhibition zones of compound 1 and 2 as shown in Table 1 being less than the standard, are potential indication of the efficacy of the tested compounds. Mutual comparison of compounds shows that 2 is more active against as compared to 1.

Table 1 *Antimicrobial activities of selected compound 1,2*

S. No	Compound	bacteria	Zone of inhibition of sample(mm)	Zone of inhibition of Std.Drug (mm
1	1	*E. coli*	14	35
		S. aureus:	11	31
		K. pneumonia:	10	28
		P. mirabilis:	13	27
2	2	*E. coli*	27	35
		S. aureus:	24	31
		K. pneumonia:	22	28
		P. mirabilis:	25	27

IV. CONCLUSION

Schiff bases are the condensation products of primary amines with aldehydes or ketones in which the carbonyl group is replaced by imine or azomethine. They are valuable class of organic compounds and able to coordinate a number of different metal ions, hence stabilizing them in a variety of oxidation states. The chemistry of Schiff's bases has attracted chemists for having active role in biological field and a wide range of biological applications such as antiviral, anticancer, anti-bacterial, antifungal, antioxidant, analgesic and antiglycation properties. Moreover, a variety of Schiff bases can inhibit the enzymatic actions due to their structural compatibility to biological systems. In the current study Schiff bases 1 and its complex 2 was synthesize and structurally characterize by commonly used spectroscopic technique (NMR) and the antibacterial activity of the synthesized compounds has been determined.

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