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## Metal Complexes of Schiff's Bases Containing Sulfonamides Nucleus: A Review.

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### ABSTRACT

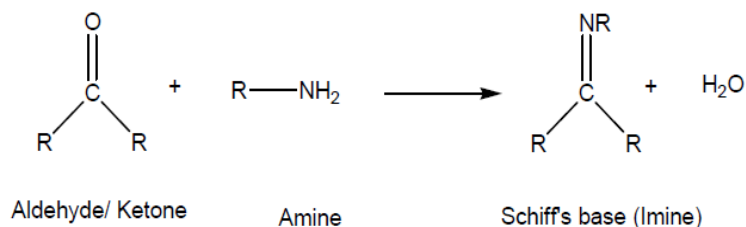
Schiff's bases are versatile ligands which are synthesized from the condensation of primary amines with carbonyl groups. Schiff's bases play an important role in Inorganic chemistry due to formation of very stable complexes with various transition and inner-Transition Metals. Transition metal complexes derived from the Schiff base ligands have widely applications. This review summarizes some metal complexes of schiff's bases derived from sulfonamide derivatives and reviewed the applications of Schiff's bases chelates in quantitative analysis.

**Keywords:** Schiff bases, Metal complexes, Quantitative analysis.

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## Overview of of Schiff's bases

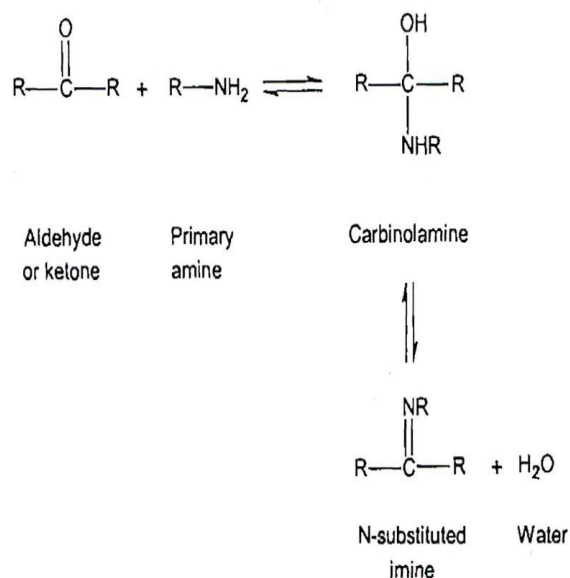
A Schiff's base is a nitrogen analog of an aldehyde or ketone in which the C=O group is replaced by C=N-R group. It is usually formed by condensation of an aldehyde or ketone with a primary amine according to the following scheme (Scheme 1):



**Scheme 1: Formation of Schiff's bases.**

Where R, may be an alkyl or an aryl group. Schiff's bases that contain aryl substituents are substantially more stable and more readily synthesized, while those which contain alkyl substituents are relatively unstable. Schiff's bases of aliphatic aldehydes are relatively unstable and readily polymerizable [1,2] while those of aromatic aldehydes having effective conjugation are more stable [3,4].

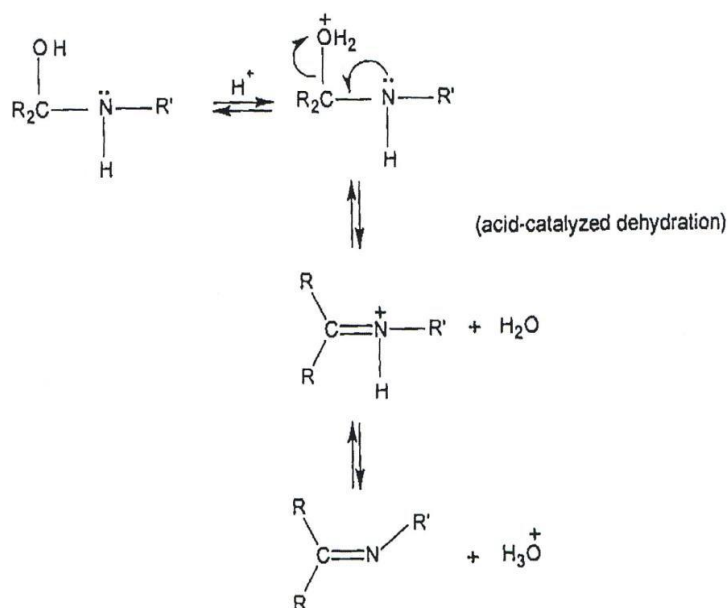
The formation of a Schiff's base from an aldehydes or ketones is a reversible reaction and generally takes place under acid or base catalysis, or upon heating (Scheme 2).



### **Scheme 2: Reversible reaction including carbinolamine as intermediate through formation of schiff's bases.**

The formation is generally driven to the completion by separation of the product or removal of water, or both. Many Schiff's bases can be hydrolyzed back to their aldehydes or ketones and amines by aqueous acid or base.

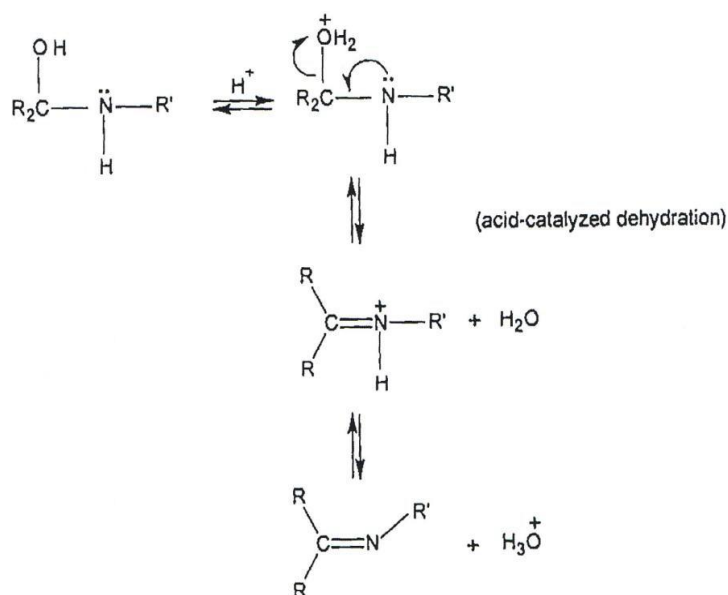
The mechanism of Schiff's base formation is another variation on the theme of nucleophilic addition to the carbonyl group. In this case, the nucleophile is the amine. In the first part of the mechanism, the amine reacts with the aldehyde or ketone to give an unstable addition compound called carbinolamine. The carbinolamine loses water by either acid or base catalyzed pathways. Since the carbinolamine is an alcohol, it undergoes acid catalyzed dehydration (scheme 3 A).



**Scheme 3A: Mechanism of Schiff's base formation step 1.**

Typically the dehydration of the carbinolamine is the rate-determining step of Schiff's base formation and that is why the reaction is catalyzed by acids. Yet the acid concentration cannot be too high because amines are basic compounds. If the amine is protonated and becomes non-nucleophilic, equilibrium is pulled to the left and carbinolamine formation cannot occur. Therefore, many Schiff's bases synthesis are best carried out at mildly acidic pH.

The dehydration of carbinolamines is also catalyzed by base. This reaction is somewhat analogous to the E<sub>2</sub> elimination of alkyl halides except that it is not a concerted reaction (Scheme 3(b)). It proceeds in two steps through an anionic intermediate.



**Scheme 3B: Mechanism of Schiff's base formation step 2.**

The Schiff's base formation is really a sequence of two types of reactions, i.e. *addition* followed by *elimination* [5].

### Schiff's bases metal complexes

Transition metals are known to form Schiff's base complexes and Schiff's bases have often been used as chelating ligands in the field of coordination chemistry. Their metal complexes have been of great interest for many years. It is well known that N, O and S atoms play a key role in the coordination of metals at the active sites of numerous metallo-biomolecules [6].

Schiff's base metal complexes have been widely studied because they have industrial, antifungal, antibacterial, anticancer, antiviral and herbicidal applications [7-9]. They serve as models for biologically important species and find applications in biomimetic catalytic reactions. It is known that the existence of metal ions bonded to biologically active compounds may enhance their activities.

There are certain metallo-elements without which the normal functioning of living organism is inconceivable. Among these metallo-elements so called, 'metals of life', four members form an island. These are Na, Mg, K and Ca, the transition elements are V, Cr, Mn, Fe, Co, Ni, Cu and Zn. These elements are present at trace and ultra trace quantities and play vital roles at the molecular level in a living system. These transition elements are known to form Schiff's base complexes.

Schiff's base metal complexes have been known since the mid nineteenth century [10] and even before the general preparation of the Schiff's base ligands themselves. Schiff's base metal complexes have occupied a central place in the development of coordination chemistry after the work of Jorgensen and Werner [11]. Etlings isolated a dark green crystalline product from the reaction of cupric acetate, salicylaldehyde and aqueous ammonia. Schiff prepared complexes of metal-salicylaldehyde with primary amines. Subsequently, Schiff prepared complexes from the condensates of urea and salicylaldehyde. Delephine prepared complexes [12] by reacting metal acetate, salicylaldehyde and a primary amine in alcohol and demonstrated a 2:1 stoichiometry.

However, there was no comprehensive, systematic study until the preparative work of Pfeiffer and associates. Pfeiffer and his coworkers [13] reported a series of complexes derived from Schiff's bases of salicylaldehyde and its substituted analogues.

The study of binuclear and polynuclear complexes of transition metal ions has received a growing attention in recent years. It has been an interesting area for chemists, physicists and biologists, since these complexes form the basis of several research fields such as bioinorganic chemistry, magneto chemistry, material science, catalysis, super conductivity and multi electron redox chemistry etc.

The transition metal complexes having oxygen and nitrogen donor Schiff's bases possess unusual configurations and structural lability and are sensitive to the molecular environment. 2-hydroxy Schiff's base ligands and their complexes derived from the reaction of derivatives of salicylaldehyde with amines have been extensively studied in great details for their various crystallographic, structural and magnetic features [14-16].

Particularly, a large number of transition metal complexes of Schiff's base ligands derived from the condensation of salicylaldehyde and 2-hydroxy-1-naphthaldehyde with various primary amines became the topic of contemporary research [17]. These Schiff's base ligands may act as bidentate N,O-, tridentate N,O,O-, N,O,N-, N,O,S-, tetradentate N,N,O,O-, hexa dentate N,N,O,O,S,S- donor ligands [18] etc., which can be designed to yield mononuclear or binuclear complexes or one-dimensional (1D), two-dimensional (2D) and three-dimensional (3D) metal-organic frame works [19].

Although several kinds of metal ions are found, metallo-proteins with transition metal ions are numerous. The main reason for the preference of transition metal ions over the other metal ions is ultimately due to their unique features such as the flexibility to adopt more than one-coordination geometries and the ability to exist in multiple oxidation states. Natural systems utilize one or both of these features for their feasible biological transformations.

Arational control of the nuclearity of transition metal complexes is important to design systems with the desired properties as some of these applications require the presence of more than one metal centre in the particular complex. Indeed, binuclear complexes may have different reactivity than mononuclear counterparts, thereby enabling transformations inaccessible to single metal ions. For instance, nucleic acid hydrolysis is postulated to be facilitated by the cooperative action of two metal ions [20].

Schiff's base ligands that are able to form binuclear transition metal complexes are useful to study the relation between structures and magnetic exchange interactions [21], and to mimic bimetallic biosites in various proteins and enzymes [22]. The complexes thus play an important role in developing the coordination chemistry related to catalysis, enzymatic reactions, magnetism and bioinorganic modeling studies [23]. In this regard, there is much interest in designing dinucleating ligands and their transition metal complexes.

Metal ions play an important role in living system both in growth and in metabolism. The active sites of the biomolecules are coordination complexes comprising of one or more metal ions. The potential relation and those of synthetic coordination complexes has contributed significantly to the emergence of interdisciplinary field of bioinorganic chemistry. The bioinorganic chemistry [24] forms the molecular basis of all possible interactions between the biological molecules and metal ions which is inturn applied in the field of medicine, biology, environmental sciences, catalysis and technology. So the research activities have been grouped as follows:

- Study of the metal coordination environment in metallo proteins, nucleic acids, carbohydrates, membranes [25].
- Study of the mechanism of reactions occurring at a metal center in enzyme.
- Study of synthetic analog for the active sites in metallo proteins (design, synthesis, structure, spectroscopy and applications like catalytic reactions and metal sequestering from waste water and deposits) [26].
- Design and study of metal containing drugs to cure or prevent diseases (36 g) (synthesis and mechanism of action).
- Removal of metal ions and metal compounds from the living system (detoxification) [27]. In all these fields, both the metal and the ligands are of important for the structure, the stability and the process that are regulated and catalysed by the metal species.

Of all the Schiff's base complexes, those derived from salicylaldimine have been thoroughly studied so far. A variety of physicochemical investigations on these complexes provide a clear understanding of their stereochemical and electronic properties. The advantage of the salicylaldimine ligand system is the considerable flexibility of the synthetic procedure, which has resulted in the preparation of a wide variety of complexes with a given metal whose properties are often dependent on the ligand structure.

#### **Applications of Schiff's bases chelates in quantitative analysis**

Jungreis and Thabet [28] have reported several applications for Schiff' bases in qualitative and quantitative classical analyses. All these applications did not cover a wide area in analytical chemistry.

Advances in analytical techniques and the development and application of new analytical reagents are as important in trace analyses as the development of analytical instruments. A number of Schiff's base chelateing agents used for the detection of metal ions can also be applied for their quantitative determination. The procedures in most cases remain similar.

The main step in the above applications is the complex formation which depends mainly on pH, temperature, cation size, and the structure of the ligand. Optimisation of these factors to enhance the stability of the complex leads to high selectivity of the developed analytical method.

## Photometric methods

Developments in photometric methods have been extensive, particularly for the determination of trace amount of metals. A number of these procedures are based on color formation resulting from the reaction between Schiff's base and the metal ion. For example, *O*-[*N*-(*O*-hydroxyphenyl)formimidoyl]phenol, known as Manganon, forms with manganese(II) at pH 9.1 to 11.6 a brown complex, the absorbance of which is measured at 428 nm.

2,2'-(2,6-Pyridinediyl BIS (Methylidyne Nitrilo) Phenol has been used by Abdennabi and Anter for spectrophotometric determination of Uranium (VI). The red color developed is measured at 500nm and the molar absorptivity is  $1.19 \times 10^4 \text{ L mol}^{-1} \text{ cm}^{-1}$ . It was found that a 100- fold excess of Barium, Strontium, Calcium, Lead, Cadmium, Chloride, Nitrate, Sulphate, and Phosphate did not interfere. The interference of some elements such as Fe(III), Cr(III), Hg(II), V(V), and Ti(V) could be eliminated by applying the ion exchange technique using the resine Dowex 1x 8 in the chloride form [29].

*N,N'*-Bis(salicylidene)ethylenediamine forms with iron(III) a complex, which is red-violet at a pH less than 5 and yellow at a pH higher than 6, with maximum wavelength 495 and 470nm respectively [28].

Tantaru G. *et al.* have prepared Salen-type Schiff's base, 1-ethyl-salicylidene-bis-ethylene diamine by condensing ethyl-*o*-hydroxyphenyl ketone with ethylene diamine. These Schiff's bases present a good capacity of complexing Mn(II) ions, resulting brown complexes. The Schiff's base forms a brown complex with Mn(II) cation, with maximum absorbance at 460 nm. The complex showed a maximum stability at pH 6.0. Spectrophotometric determination of Mn(II) using this Schiff's base as reagent were successfully applied to pharmaceutical products containing Mn(II) cation [30].

*N,N*-bis(3-methylsalicylidene)-ortho-phenylene diamine (MSOPD), has been synthesized and used in the spectrophotometric determination of nickel. At pH 8, MSOPD can react with nickel ion at room temperature to form a 1:1 complex. The apparent molar absorptivity is  $9.5 \times 10^4 \text{ mol}^{-1} \text{ cm}^{-1}$  at 430 nm. With a detection limit of  $1.36 \times 10^{-8} \text{ M}$ . Nickel in some natural food samples has been determined [31].

*N,N*-bis(pyridinylmethylene)ethylenediamine was studied by Leyva and Palma. The optimum experimental conditions for the spectrophotometric determination of copper were established. Beer's law is obeyed between 1 and 10 ppm of copper. The precision of the procedure, expressed in terms of relative standard deviation, was 0.31% [32].

Asuero A. G. has reviewed Schiff's bases derived from biacetyl as analytical reagent, more than 50 reagents and their related cation, method used, and medium have been reported [33].

Number of spectrophotometric determinations have been carried out, for biacetyl bis(4-phenyl-3-thiosemicarbazone) (BBPT). It has been used as a reagent for the extractive spectrophotometric determination of cadmium and bismuth. Analytical applications of biacetyl bis(4-phenyl-3-thiosemicarbazone) and bipyridylglyoxal bis(4-phenyl-3-thiosemicarbazone) has been reported [34].

Trace levels of palladium(II) has been determined by Asuero *et al.* The method relies upon the extraction of palladium(II)-biacetylmonoxime 2-pyridylhydrazone (BMPH) from aqueous acidic solution into chloroform to form a purple-reddish complex. The molar absorptivity of the Pd-BMPH complex is about  $7500 \text{ L mol}^{-1} \text{ cm}^{-1}$  at 560 nm in the chloroform extract.

## Fluorometry

Fluorometric methods often provide excellent means for the detection and determination of inorganic ions. The reagents employed to produce fluorescence are often highly selective and very sensitive. In most cases a chelate is formed with the metal. There is often a dependence of fluorescence on the pH similar to that of acid-base fluorescence indicators. The analytical importance of such indicators lies in the fact that they make possible acid-base titrations in colored solutions when the use of conventional indicators would be precluded. Holzbecher reported that Schiff's bases obtained from salicylaldehyde and aniline fluoresce in the alkaline medium and therefore, can be used for titration of acids with bases.

He also proposed *O*-[*N*-(*O*-hydroxyphenyl)formimidoyl]phenol, for quantitative determination of aluminium.

Sabry studied the fluorescence properties of Schiff's bases derived from 2-acetylbutyrolactone and spectrofluorimetric determination of primary amine-containing compounds. 2-Acetylbutyrolactone (ABL) has been characterized for use as a fluorogenic reagent for the spectrofluorimetric determination of primary amines. The reagent forms strongly fluorescent Schiff's bases upon the reaction with primary amines in acid-catalyzed aqueous solutions or in dimethylformamide (DMF) [35].

Determination of trace cadmium with GBHA has been developed by Dong Gai. The cadmium ion can form a stable chelate with GBHA, having a ratio of 1:3 in the 12.0 -13.0 pH range with maximum excitation and emission wavelengths are 227.4 nm and 320.0 nm for the cadmium chelate, respectively, and fluorescence intensity from 20 to 150 min. Linear function of concentration in the range (1.0-10.0) mg ml<sup>-1</sup> of cadmium and the detection limit is 0.65 mg ml<sup>-1</sup> of cadmium. [36].

### Schiff's bases as potentiometric sensors

Since the 1930s, potentiometric membrane sensors have found great practical applicability in different fields. The response mechanism of these sensors is based on the measurement of a potential under a zero current regime or a under a low electrical current flow. Potentiometric membrane sensors, which have been designed based on molecular recognition, contain a molecule that selectively recognizes another target species through various molecular interactions. As it is widely known, potentiometric electrodes possess as advantages the direct, simple, rapid, inexpensive and selective detection of ionic activities [37].

Ganjali *et al.* have prepared potentiometric sensors for Dy(III) based on a Bis-pyrrolidene Schiff's bases, the electrode has been also used in the potentiometric determination of Fluoride ions in mouthwash by the titration against Dy(III) They also prepared a novel Bromide ion sensor based on Iron(III)-salen, this sensor has high Bromide selectivity over a wide variety of organic and inorganic anions, specially iodide, chloride and hydroxide ions [38].

A large number of different Schiff's base ligands have been used as cation carriers in potentiometric sensors as they have shown excellent selectivity, sensitivity, and stability for specific metal ions [39-48].

### High-Performance Liquid Chromatography

In the last few years the rapid development of high-performance (pressure) liquid chromatography (HPLC) has also extended the possibilities for chromatographic methods in inorganic analysis. In particular liquid chromatographic methods in columns are of great importance for those inorganic compounds which are not suitable for the usual gas chromatographic methods because of low volatility or low thermal stability.

Chromatographic methods are very suitable for the separation and determination of extractable metal chelates.

Different types of ligands or groups of compounds are suitable for HPLC such Schiff's base chelates, hydrazones, dithizonates, and metal dithiocarbamates. For these groups of substances principally reversed-phase and adsorption systems are suitable; separations by reversed- phase systems are very well Reproducible [49-51].

The separation of neutral copper and nickel chelates of two representative Schiff's base ligands, *N,N'*-ethylenebis(acetylacetoneimine) and *N,N'*-ethyfenebis(salicylaldimine) is reported on a column of 10 micrometer diameter silica. Both pairs of chelates are well resolved with good peak shape and efficiencies when the mobile phase is 4 : 1 methylene chloride-acetonitrile. An HPLC method for the determination of scandium(III) was developed, with diacetyl-*N,N*-bis(4- hydroxybenzoylhydrazone) (DBHB) as a pre-column chelating agent. Tetradentate DBHB formed a 1 : 1 chelate with Sc(III) ion. The Sc(III)-DBHB chelate was separated on a C18-silica gel column with a mobile phase of acetonitrile-water (30+70m/m) containing tetramethylammonium bromide and hexamethylenetetramine buffer.

Kanbayashi. et al. have developed a method for highly selective determination of trace amounts of  $\text{Co}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Ni}^{2+}$  and  $\text{V}^{5+}$  ions by reversed-phase high-performance liquid chromatography (HPLC) and spectrophotometric detection has been accomplished without the addition of a chromogenic reagent to the eluent. Six tetradentate Schiff-base ligands, all *N,N'*-*O*-phenylenebis(salicylaldehyde) (PBS) derivatives, were synthesized and made to react with the metal ions [52].

## Sulfonamides

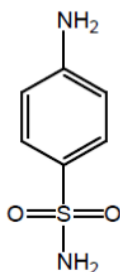
### Sulfonamides Defined

Sulfonamides are compounds that contain sulfur in a  $\text{SO}_2\text{NH}_2$  moiety directly attached to a benzene ring. Many medications contain sulfur but are not sulfonamides, e.g., amoxicillin, captopril, omeprazole, spironolactone, sulfates and sulfites. There is no risk of cross-reactivity between these substances and sulfonamides. Sulfonamides can be divided into two groups; the antibiotics (eg, sulfamethoxazole, sulfisoxazole, sulfacetamide) and the non-antibiotic sulfonamides (e.g., thiazides, furosemide, glyburide, sumatriptan, celecoxib). Certain chemical structures unique to the antibiotic group are implicated in the production of hypersensitivity reactions - an arylamine moiety at the N4 position and substitutions at the N1 position of the benzene ring. Table 1 explains Commonly used sulfonamides and non-sulfonamide alternatives.

**Table 1: Commonly used sulfonamides and non-sulfonamide alternatives**

Drug class	Sulfonamide drugs	Alternative drugs
Antibiotics	Silver sulfadiazine, sulfacetamide, sulfadiazine, sulfadoxine, sulfamethoxazole, sulfapyridine, sulfasoxazole	Aminoglycosides, cephalosporine, clindamycin macrolides, nitrofurantoin, peniciline, fluroquinolones, tetracycline, trimethoprim
Anti-inflammatory agents	Celecoxib, valdecoxib	Rofecoxib, non-selective NSAIDs
Anti-glaucoma agents	Acetazolamide, brinzolamide, dorzolamide, methazolamide	Ophthalmic beta-blockers, prostaglandin analogues, apracionidine, brimonidine, dipvefrin
Diuretics	Bumetanide, chlorthalidone, chlorothiazide, diazoxide, furosemide, hydrochlorothiazide, indapamide, metoiazone, torsemide.	Amiloride, mefformin, thiazolidinediones, nateglinide, repaglinide.
Hypoglycemics	Chlorpropamide, tolbutamide, glyburide, gliclazide, glimepiride.	Acarbose, metformin, thiazolidinediones, nateglide, repaglinide.
Inflammatory bowel disease therapy	sulfasalazine	5-ASA products

### The Origin of Sulfonamides



**Figure 1: General structure of sulfonamide.**

In 1936, a year after Domagk's discovery of the anti-streptococcus activity of the dye prontosil, Ernest Fourneau of the Pasteur Institute in Paris discovered that prontosil breaks down in the human body to produce sulfanilamide which is the active agent that kills streptococcus bacteria. Fourneau's discovery triggered a flurry of research on structural derivatives of sulfanilamide which resulted in development of a family of highly



successful antibiotics that have saved millions of lives (Figure 1 explains the general structure of sulfonamide)[53].

Sulfapyridine was shown to be effective against pneumonia in 1938. Sulfacetamide found highly successful use in fighting urinary tract infections starting in 1941. Succinoylsulfathiazole has been used against gastrointestinal tract infections since 1942. Sulfathiazole was used very effectively during World War II to fight infection in soldiers with battle wounds. Sulfanilamide itself, a potent antibiotic, never gained widespread use due to its greater human toxicity versus its various derivatives. Figure 2.

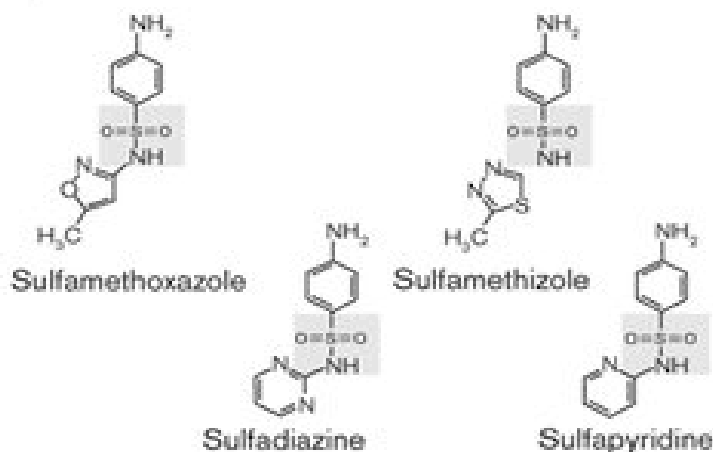
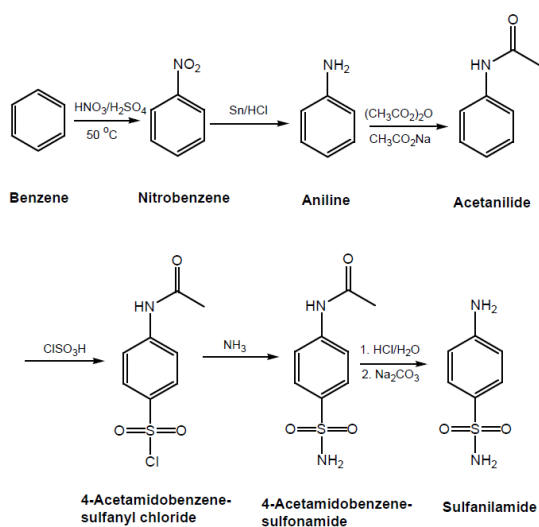


Figure 2: Some derivative of sulfonamide.

The total synthesis of sulfonamide from benzene can be carried out in six steps using reactions that are very familiar to intermediate level organic chemists. In addition to providing a great example of the synthetic utility of these reactions, the synthesis demonstrates the use of protecting group chemistry, and taking advantage of steric and electronic directing effects (in electrophilic aromatic substitution) and differing rates of hydrolysis to optimize the yield of the desired product. The synthesis to be performed here will start from nitrobenzene to make sulfonamide in five steps (Scheme 4).



Scheme 4: Synthesis of sulfonamide from benzene

## Some metal complexes of Schiff's base derived from sulfonamides

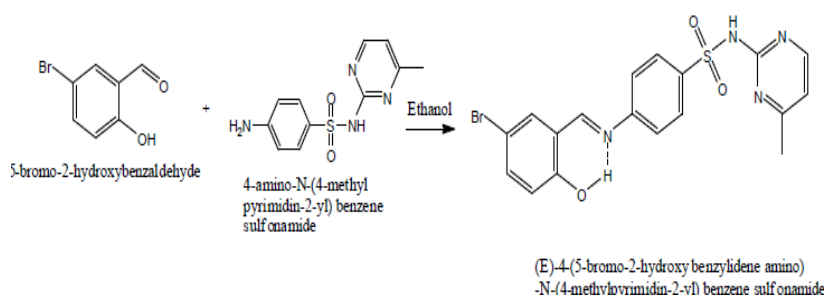
Sulfonamides were the first drugs found to act selectively and could be used systematically as preventive and the therapeutic agents against various disease. Sulfur ligands are awidespread among coordination compounds and are important components of biological transition metal complexes which posses many applications such as diuretic, antiglaucoma or antiepileptic drugs among others. First row transition metals such as Cu, Zn, Co, etc. compounds have attracted much attention due to their biological importance. It has been reported that the biological activity of sulfur containing ligand increase on complexation. many aldehydes are known to be potential inhibitors for DNA synthesis; therefore, if a salicylaldehyde, benzaldehyde and furfural moiety is coupled with sulfonamides the resulting compound sulfanomide-imine may show enhanced biological activity. These factors propted us to carry out astudy for synthesis of sulfonamides-imine (Schiff's base) and its complexes with Cu, Ni, and Co metal ions [54].

### Schiff's base derived from (E)-4-(5-bromo-2-hydroxybenzylideneamino)-N-(4-methylpyrimidin-2-yl)benzenesulfonamide with Cu(II), Co(II), and Ni(II)

Rama I. *et al.* synthesis this complex and found that the newly synthesised Schiff's base ligand and its complexes are brightly coloured and very stable at room temperature. They are insoluble in organic solvents like ethanol, methanol and chloroform and soluble in solvents like DMF, Dioxane and DMSO.

The synthesised ligand (Scheme 5) and its metal complexes (Figure 3,4) were tested against two gram-positive (*S. aureus*, *Bacillus subtilis*) and two gram-negative (*E.coli*, *Klebsiella sp.*) bacterial strains by disc diffusion method. The results were compared with those of the standard drug ciproflaxin.

All the complexes showed a wide range of activities and the nickel complex is significantly active against all bacterial strains whereas cobalt complex shows less activity. The antifungal activity of the compounds was tested against *A.niger* and *Candida albicans* and the standard used was nystatin. Majority of the synthesised compounds showed good antifungal activity against these fungal strains. When compared to the cobalt and copper complexes, nickel complex exhibits promising activity. It is observed that the antimicrobial activities of all the complexes are found to be increased after chelation [55].



Scheme (5): preparation of ligand

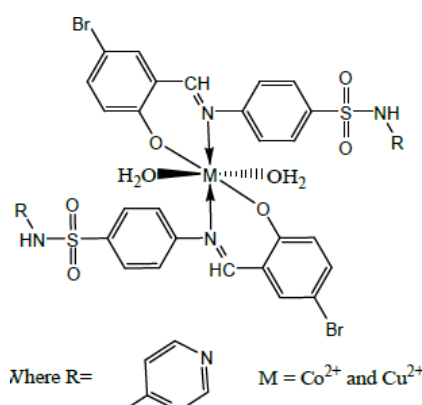


Figure 3: Structure of octahedral complexes

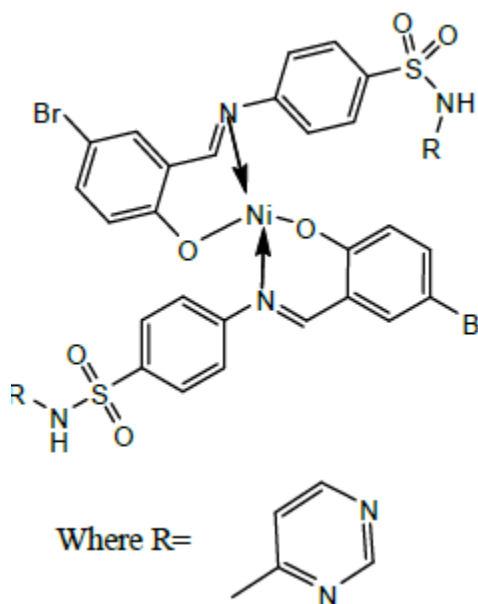
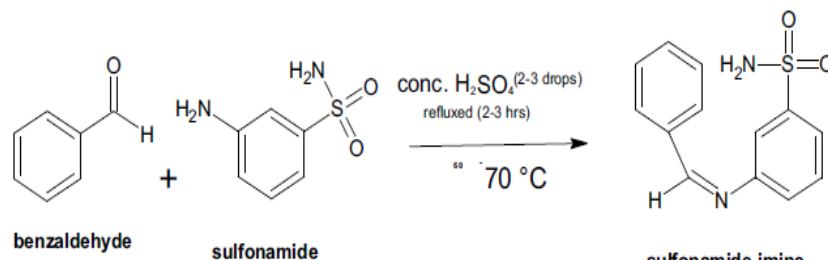


Figure 4: Structure of Nickel (tetrahedral) complex.

#### Schiff's base derived from sulfonamide-imine with Ni(II), Co(II), Cu(II)

Nida I. *et al.* synthesized the sulfonamides-imine derived from benzaldehyde and sulphanomide (Scheme 6), and study their complexation behavior and antibacterial activities in complexed and uncomplexed states against *E.coli* and *Salmonella thphae*. Figure 5. They were observed that the metal chelates are more antibacterial than uncomplexed ligand [54].



Scheme (6): preparation of ligand

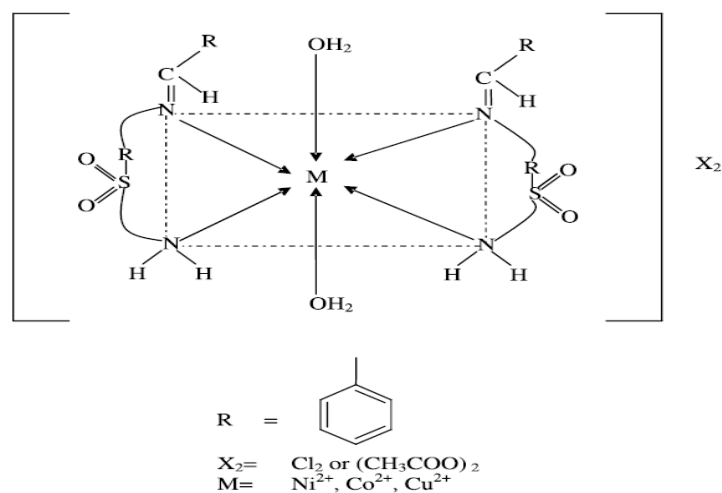


Figure 5: Structure of complex.

**Schiff's base derived from *N*-[(*E*)-(5-Bromo-2-Hydroxyphenyl) Methylidene]-4-Nitrobenzenesulfonamide with Cu(II), Zn(II), Co(II), and Ni(II)**

Ali A. *et al.* were prepared Metal complexes of Cu (II), Co (II), Ni (II) and Zn (II) of Schiff's based derived from 5-bromo-2- hydroxybenzaldehyde and 4-nitrobenzenesulfonamide and studied the biological screening effect of Schiff's base and their metal complexes are studied against gram positive and gram negative bacteria. The biological activity show shows significant activity of metal complexes as compared to that of ligand.. The structure of the Schiff's base ligand and complex shown in (Figure 6-7) [56].

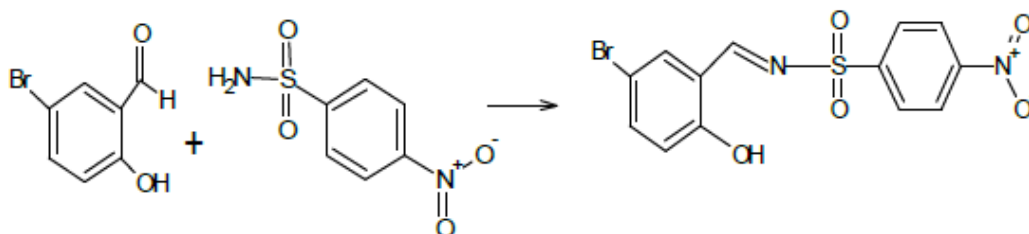
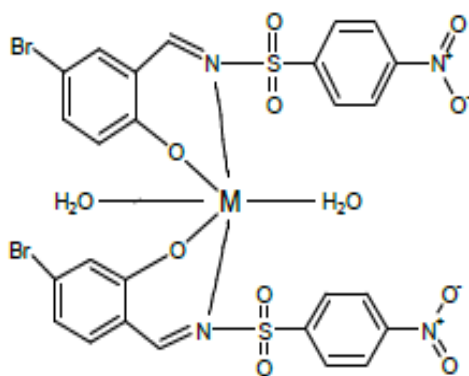


Figure (6): The structure of ligand.



where M = Cu (II), Co (II), Ni (II) and Zn (II)

Figure 7: Probable structure of metal complexes

**Schiff's base derived from [4-amino-*N*-(5-methyl-3-isoxazolyl) benzenesulfonamide] with Cu(II) and Hg(II)**

Bharti J. *et al.* synthesized of Copper(II) and Mercury(II) complexes with Schiff's base of sulfamethoxazole [4-amino-*N*-(5-methyl-3-isoxazolyl) benzene sulfonamide]. (Figure 8-10) [57].

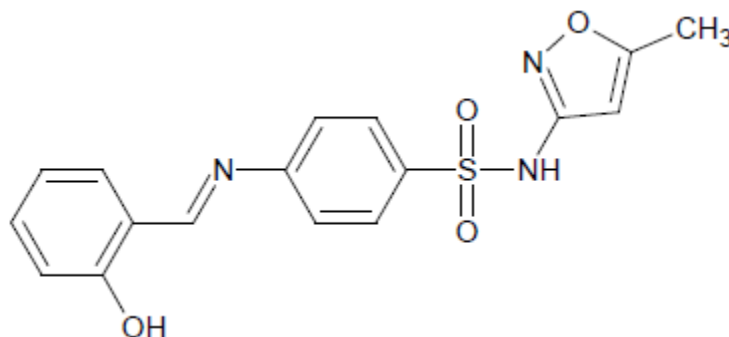


Figure 8: Structure of Sulfamethoxazole-Salicyladimine (Schiff's base).

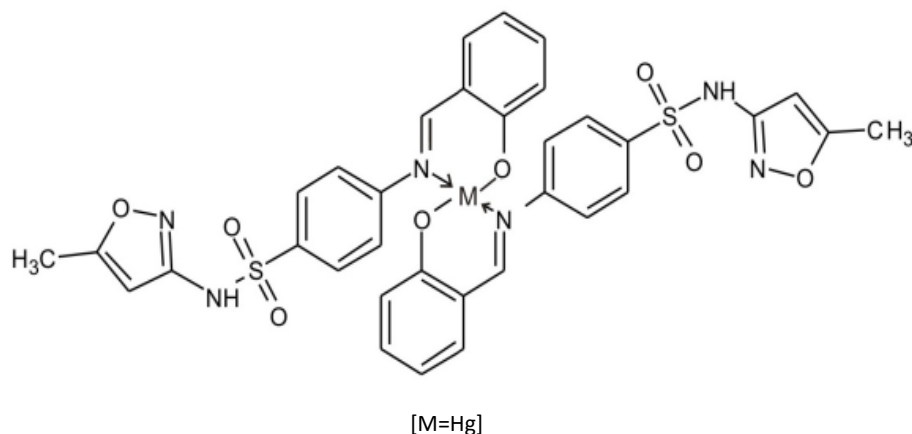


Figure 9: Structure of SMZ-SD-Hg complex.

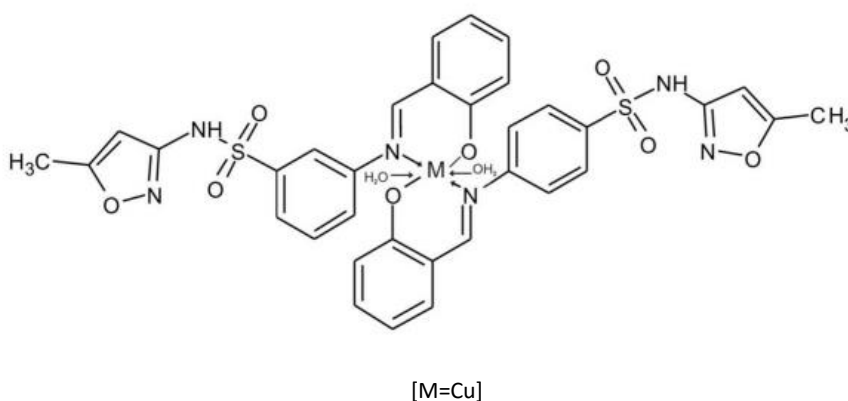


Figure 10: Structure of SMZ-SD-Cu complex.

#### Schiff's base derived from [4-amino-*N*-(5-methyl-3-isoxazolyl) benzenesulfonamide with Co(II) and Fe(II)

Bharti J. *et al.* synthesized of Co(II) and Fe(II) complexes with Schiff's base of sulfamethoxazole [4-amino-*N*-(5-methyl-3-isoxazolyl) benzenesulfonamide], they found from the analytical, spectral and antibacterial data, it can be concluded that the synthesized complexes are stable and the biological activity of the ligand is enhanced when it is presented in the form of metal complex Figure (11-12) [55].

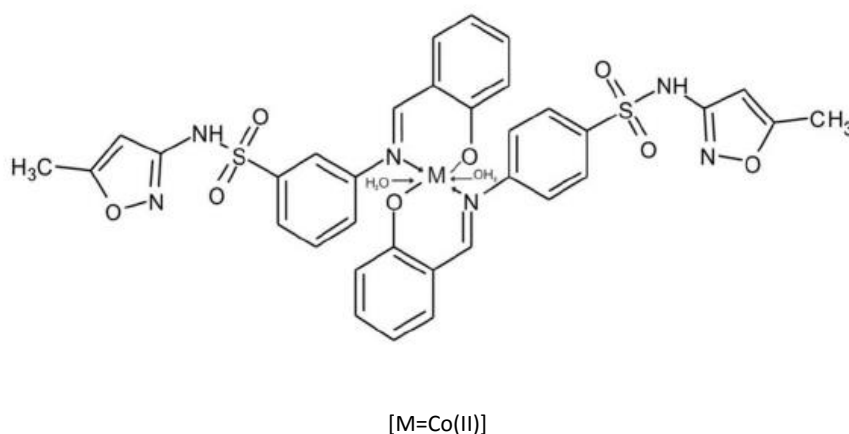


Figure 11: Structure of Sulfamethoxazole-Salicyladimine-Co complex.

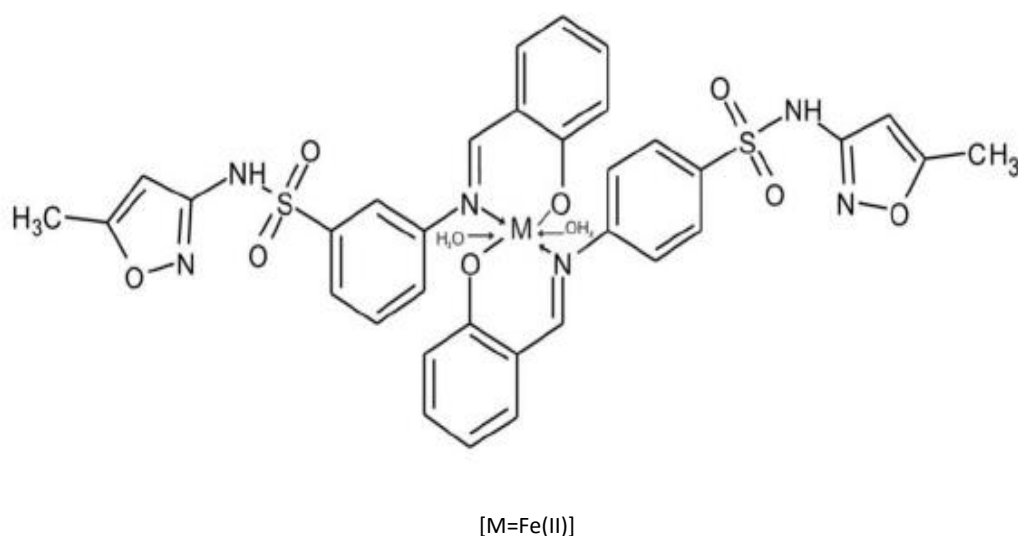
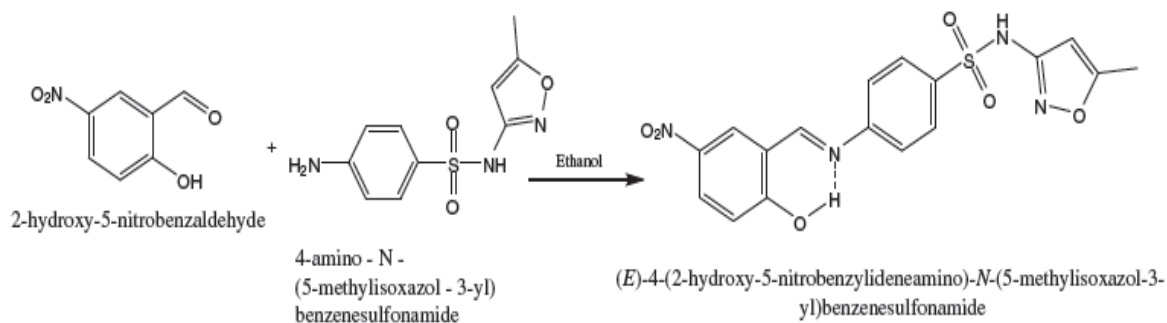


Figure 12: Structure of Sulfamethoxazole-Salicyladimine-Fe complex.

**Schiff's base derived from (*E*)-4-(2-hydroxy-5-nitrobenzylideneamino)-*N*-(5-methylisoxazol-3-yl)benzenesulfonamide with Cu(II)**

Rama I. et al. synthesized copper complex of the Schiff's base ligand (Scheme 7-8), which is a derivative of sulfamethoxazole and 5-nitro salicylaldehyde. The structure of the complex corresponds to a six-coordinate monomeric Cu(II) complex, the binding set includes two phenolato oxygens, two imine nitrogens of the ligand and two carbonyl oxygen atoms of the solvent DMF, and the geometry being distorted octahedron. The analysis of the EPR spectra and magnetic susceptibility data revealed a clear correlation with the structure of the analyzed complex and the longer coordination bond in axial position is described by the Jahn-Teller effect. The biological activity of the ligand is enhanced after complexation with metal [58].



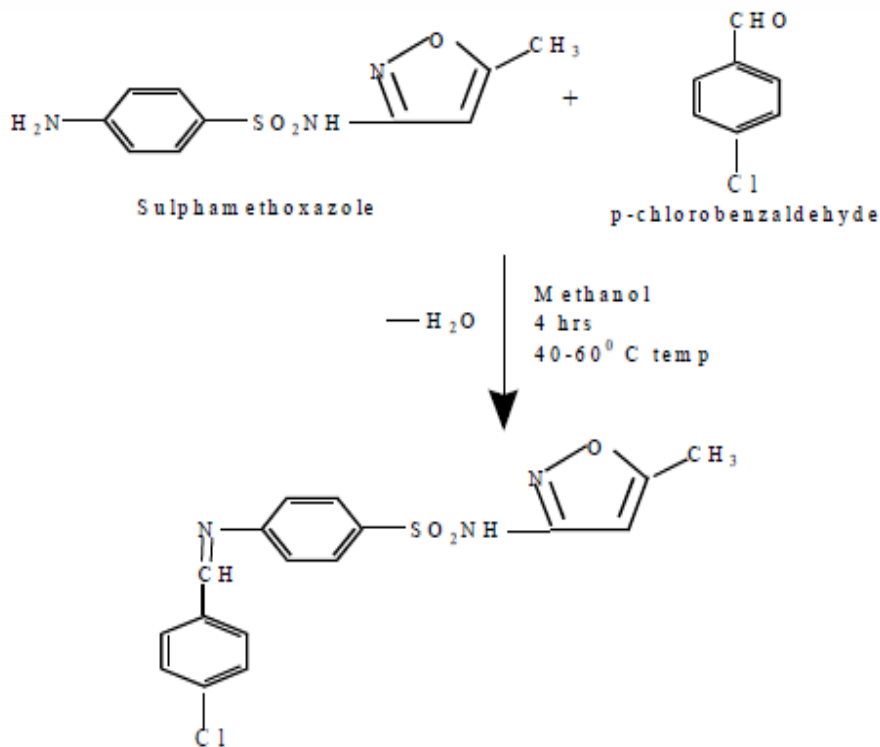
Scheme (7): Preparation of ligand.



Scheme 8: Synthesis of copper complex.

**Schiff's base derived from [4-amino-*N*-(5-methyl-3-isoxazolyl) benzenesulfonamide] with Zn(II), Ni (II), Co(II), and Mn(II)**

Sunil J. *et al.* were prepared new Schiff's bases by taking *p*-Chlorobenzaldehyde with Sulphamethoxazole and their complexes, as shown in Scheme (9) and Figure 13.



Scheme (9): synthesis of ligand.

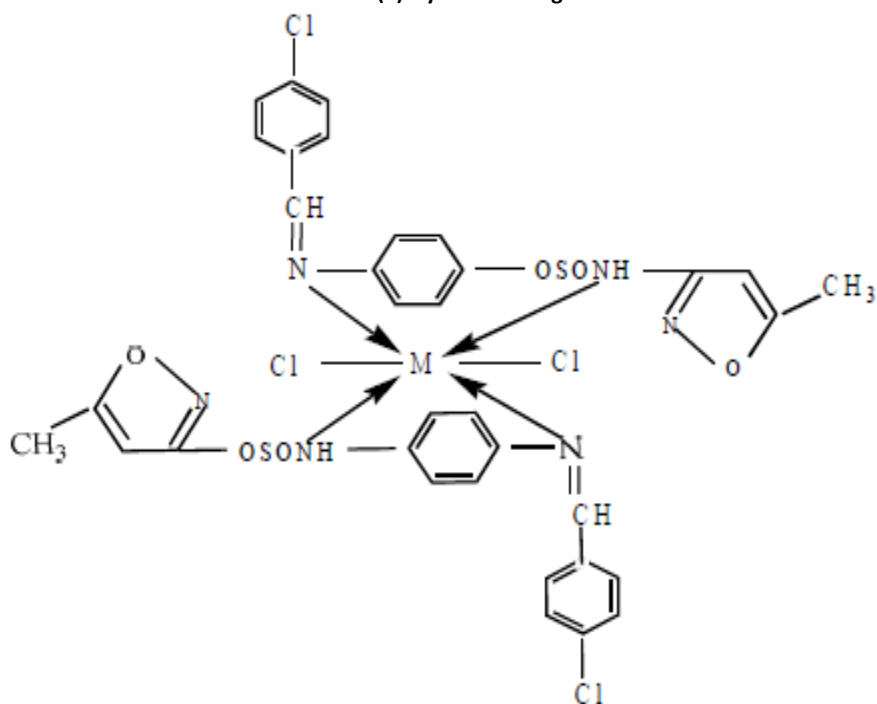
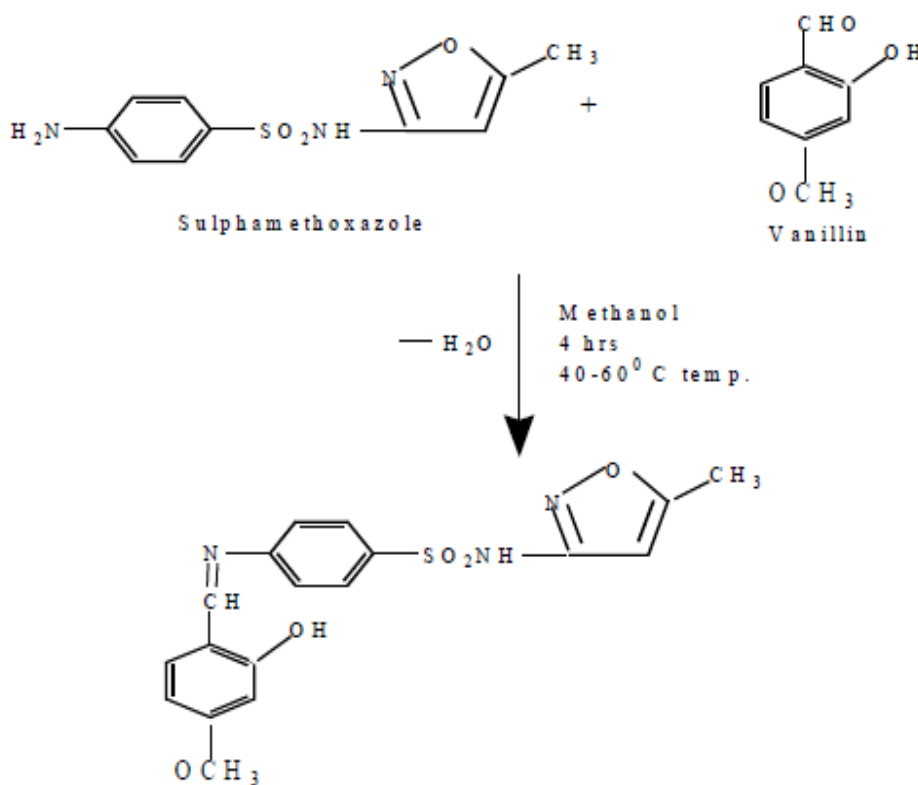


Figure 13: Metal complexes.

**Schiff's base derived from [4-amino-N-(5-methyl-3-isoxazolyl) benzenesulfonamide] with Zn(II), Ni (II), Co(II), and Mn(II)**

Sunil J. *et al.* were prepared new Schiff's bases by taking Vanillin with Sulphamethoxazole and their complexes, as shown in Scheme 9 and Figure 13.



Scheme (10): synthesis of ligand.

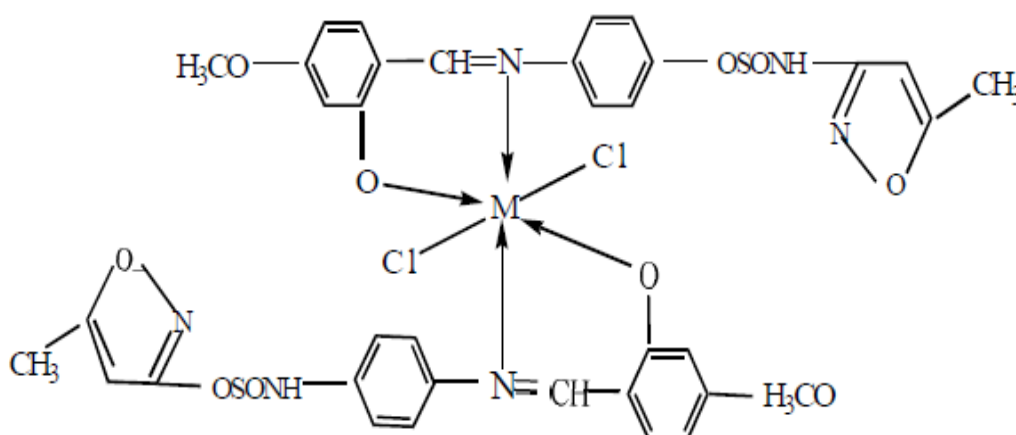


Figure 14: Metal complexes.

Schiff's base and their metal chelates were evaluated for their antibacterial activities against bacteria Gram (-) like *E. coli* and Gram (+) like *S. aureus*, *M. luteus* and *B. licheniformis*. The result of this investigation supports the suggested structure of the metal complexes. A square planar structure was suggested for all the



complexes, the Schiff's base ligands were found to be biologically active and their metal complexes display enhanced antimicrobial activity against one or more strains, chelation tends to make the ligands act as more powerful and potent bactericidal agent [59].

### CONCLUSION

The chemistry of Schiff bases is a field that is being noticed. Schiff base ligands are considered privileged ligands because they are easily prepared by a simple one pot condensation of an aldehyde and primary amines. These compounds and their metal complexes had a variety of applications including clinical, analytical, industrial they also play important roles in catalysts. This review touched on the uses of Schiff's bases in analytical chemistry field is sensors or solid phase extraction sorbents because this application promised in nowadays.

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