



CHEMICAL, BIOCHEMICAL AND ALLIED ASPECTS OF SCHIFF BASE AND ITS TRANSITION AS WELL AS NON TRANSITION METAL COMPLEXES

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ABSTRACT

Schiff bases derived from a large number of carbonyl compounds and amines are an important class of ligands that coordinate to metal ions via azomethine nitrogen and have been studied extensively. Schiff bases and their transitional metal complexes play an important role in the field of coordination chemistry compounds research since their discovery. Schiff bases and their metal complexes exhibit various pharmacological applications being antibacterial, antimicrobial, anticancer, antiviral, and anti-inflammatory. The rapid development of these ligands resulted in an enhanced research activity in the field of coordination chemistry leading to very interesting conclusions. In the present review we have discussed the application of Schiff base metal complexes. This review deals with the applied aspects of Semicarbazones, Thiosemicarbazones, Dithiocarbazate, and Isonicotinoyal hydrazones metal complexes. The metal complexes of Schiff base ligands exhibit good biological and pharmacological as well as industrial applications as compared to their parent ligands.

KEYWORDS

Schiff Base, Semicarbazones, Thiosemicarbazones, Dithiocarbazate, Isonicotinoyal hydrazones.

1. INTRODUCTION

The chemistry of Schiff base complexes has developed rapidly in the last 30 years, solving problems related to stereochemistry and electronic factors largely govern the reactivity and stability of chelate compounds [1]. The stereochemistry and electronic structure of chelates determine many properties [2], reactivity and ability to form adducts. These properties are important for understanding many catalytic processes and phenomena occurring in living organisms [3]. In chemistry, Schiff bases are the basic units in certain dyes, whereas, some are used as liquid crystals. The rapid development of these ligands resulted

in an enhanced research activity in the field of coordination chemistry leading to very interesting conclusions. Many biologically important Schiff bases have been reported in the literature possessing, antibacterial [4], antifungal [5], antimicrobial [6], anticonvulsant [7], anti HIV [8], anti-inflammatory [9] and antitumor [10-11] activities. Schiff bases derived from a large number of carbonyl compounds and amines are an important class of ligands that coordinate to metal ions via azomethine nitrogen and have been studied extensively [12]. Schiff base complexes derived from 4-hydroxysalicylaldehyde and amines have strong anticancer activity e.g. Ehrlich ascites carcinoma (EAC) [13]. It is well known that some drugs have increased activity when administered as metal complexes rather than as free organic compounds [14]. Schiff base complexes are important for designing metal complexes related to synthetic and natural oxygen carriers [15]. Schiff bases and their structural analogues, as ligating compounds containing acyclic and cyclic imine C=N bonds, are of great importance in modern coordination chemistry [16]. Interest in metal complexes of these ligands [17] is related to wide variability of their fine structure and obtaining of polyfunctional materials. Among them, we note luminescent complexes [18], magnetoactive [19] and liquid crystal [20] structures, chemosensors [21-22] and other useful metal containing azomethine compounds [23]. Schiff bases are important class of compounds in medicinal and pharmaceutical field. They show biological applications including antibacterial, antifungal and antitumor activity. Diamino tetradentate Schiff bases and their complexes have been used as biological models to understand the structures of biomolecules and biological processes. The interaction of metal complexes containing N₂O₂ Schiff base ligands has been thoroughly considered. DNA binding is the critical step for DNA activity [24].

2. SCHIFF BASE METAL COMPLEXES AND THEIR APPLICATIONS

Metal complexes of Schiff bases represent an important class of coordination compounds [25]. Schiff bases containing polyfunctional groups produce stable complexes of transition, non-transition, inner-transition and actinide metal ions. The growing importance of the Schiff bases and their metal complexes in modern coordination chemistry is attributable to recent observations about their antibacterial, antifungal and oxygen carrier properties. Investigations on the interaction between transition and non-transition metal complexes and DNA has attracted much interest due to the potential uses of these metal complexes as chemotherapeutic drugs and tools in molecular biology [26]. Many kinds of metal complexes were synthesized in order to study their abilities of recognition and cleavage toward DNA [27]. Among them, Schiff base metal complexes are a kind of attractive reagents due to their special activities in pharmacology and physiology. Scientists paid a great interest in the synthesis, structures and DNA cleavage abilities of Schiff base metal complexes in recent years [28]. Copper(II) and nickel(II) are important life elements and play an important role in biological chemistry especially because of their interesting reactivity and catalytic activity. The copper(II) complexes derived from the Schiff bases 1-[(2-diethylaminoethylimino)methyl] naphthalen-2-ol and 2,4-dibromo-6-[(2-diethylaminoethylimino)methyl] phenol (Figure 1) have been reported by Wang *et al.* [29]. The urease inhibitory properties of these complexes were determined.

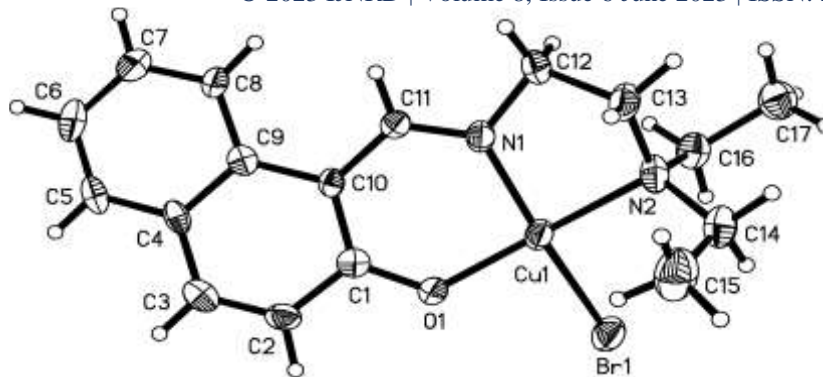


Figure 1: The structure of Cu(II) complex

Parnau *et al.* [30] synthesized Schiff bases by the condensation of isatin with diamines: ethylenediamine (HL':2IZTen), *o*-phenylene- diamine (HL'':2IZTfen) or tolylene (HL''':2IZTtol) (Figure 2).

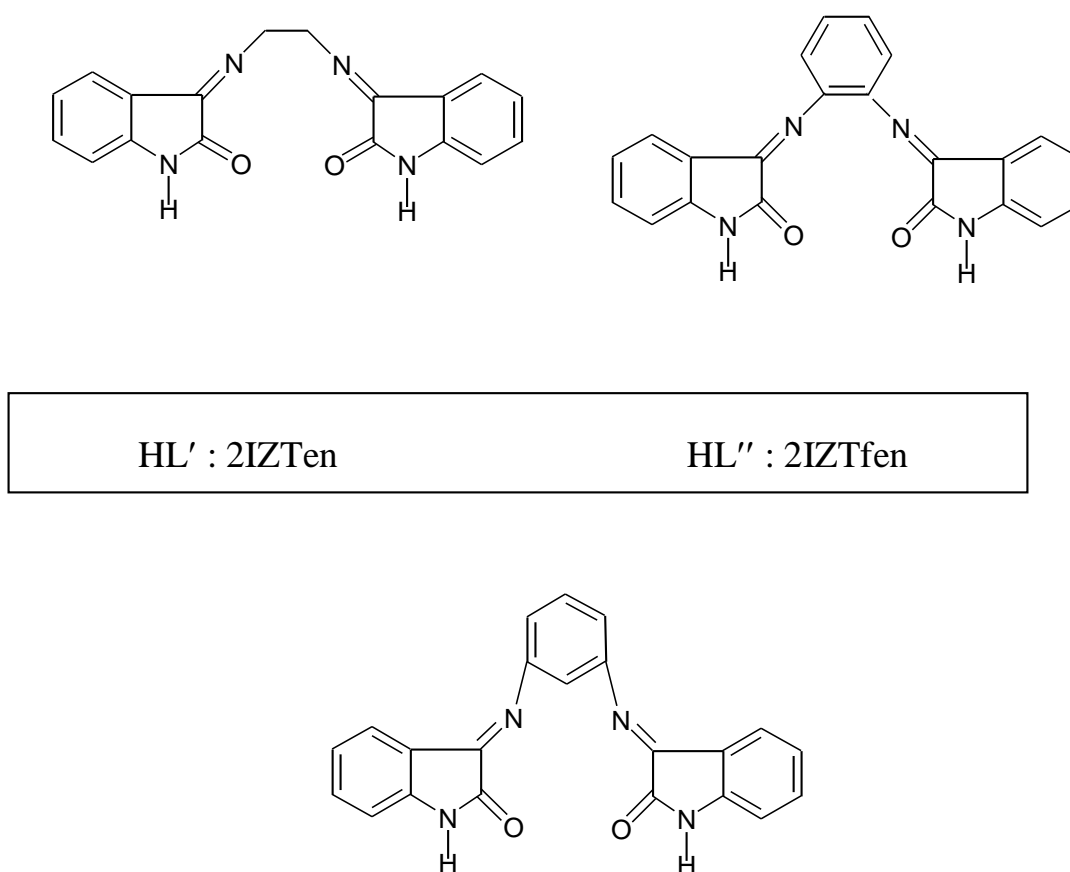
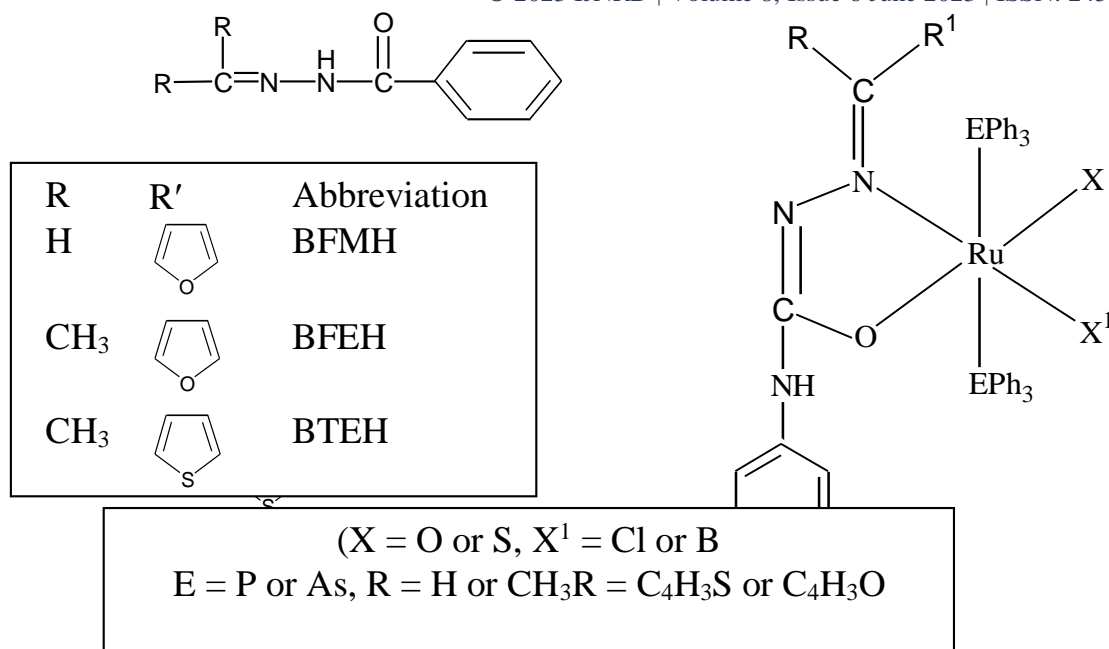


Figure 2

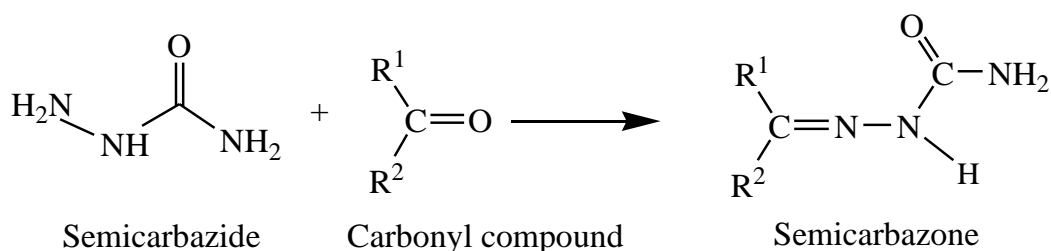
Balasubramanian *et al.* [31] synthesized and characterized few monobasic bidentate Schiff bases and their metal complexes by the condensation of benzhydrazide with furfuraldehyde, 2-acetylfuran and 2-acetylthiophene and studied their antimicrobial activity (Figure 3).

**Figure 3**

The metal complexes of hydrazinecarbothioamides, hydrazinecarboxamides, benzothiazolines and hydrazones Schiff bases have aroused considerable interest in view of their industrial and biological interest [32]. Many of these compounds possess a wide spectrum of medicinal properties. It is well established fact that these compounds have been shown to possess antimicrobial, antitubercular [33], antimalarial [34], antiviral [35] and antifertility activities [36]. The multifarious roles of transition metals in biochemistry suggest that considerable potential exists for the development of new chemistry with these metals in ligand system, specifically designed to serve these role.

2.1 SEMICARBAZONES AND THEIR METAL COMPLEXES

It is well known that Schiff base-derivatives containing N and O atoms as donor atoms can act as good chelating agents for the transition metal ions [37]. The transition metal complexes having oxygen and nitrogen donor Schiff bases possess unusual configuration, structural lability and are sensitive to molecular environment [38]. In recent years there has been considerable attention focused on the chemistry of metal complexes of Schiff bases containing nitrogen and oxygen [39]. Semicarbazones are usually obtained by the condensation of semicarbazide with suitable aldehyde and ketones, may be named by adding the class name 'semicarbazone' after the name of the condensed aldehyde, RCHO or ketone, R¹R²C=O as shown in Figure 4.

**Figure 4**

Semicarbazones are versatile ligands in both the neutral and anionic forms. Although the proton lost by the anions formally belongs to the hydrazine –NH group, the anion is usually represented in Z-configuration (Figure 5 and 6). It should nevertheless be borne in mind that, as in the neutral molecules, the π -charge is actually delocalized [40].

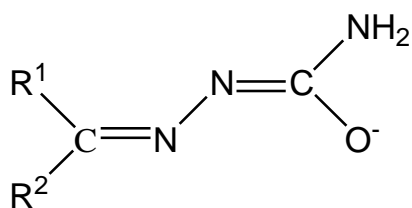


Figure 5

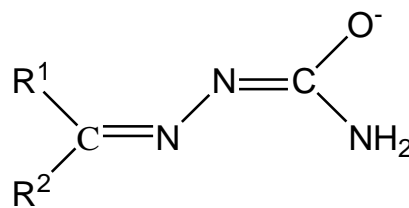


Figure 6

Z.Yu *et al.* [41] synthesized a linear trinuclear nickel complex containing the ligand, N,N'-bis(salicylidene)-1,3-diiminopropane(H₂Salpn). (Figure 7)

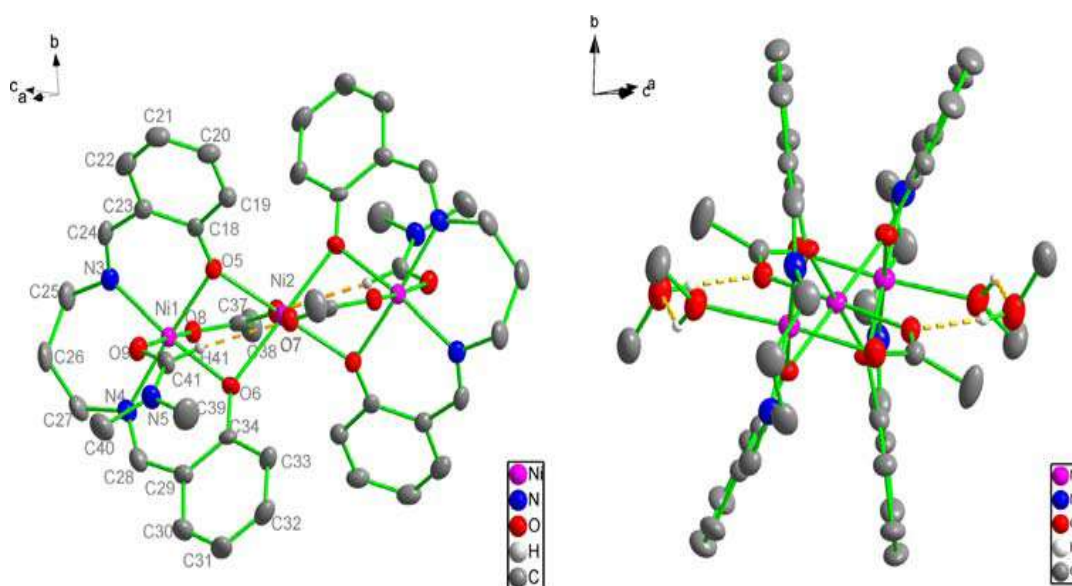


Figure 7: ORTEP diagram of the Ni(II) complex

Eugênio *et al.* [42] have reported recently synthesis and characterization of heterobimetallic compounds from semicarbazones of formylferrocene and acetylferrocene with organotin(IV). (Figure 8)

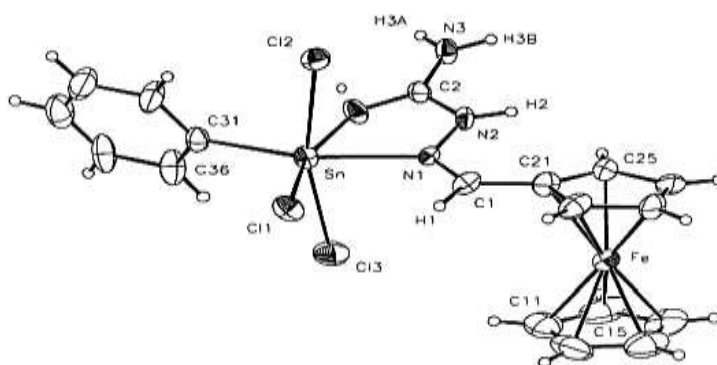


Figure 8

Leovac *et al.* [43] characterized pyridoxal semicarbazone (Figure 9) and its metal complexes and studied their biological activity.

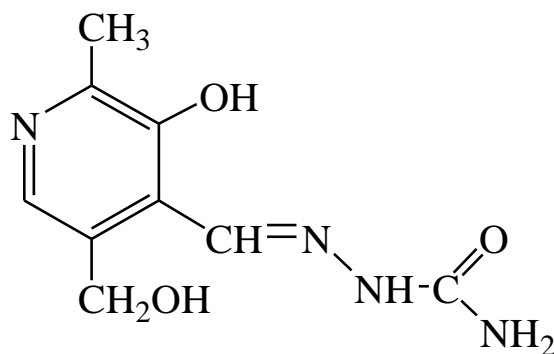


Figure 9

2.2 THIOSEMICARBAZONES AND THEIR METAL COMPLEXES

Coordination chemistry of thiosemicarbazides has been studied in the past due to their mixed hard-soft donor character and versatile coordination behavior. Thione compounds can act as anticarcinogenic or antitumor reagents. In their metal complexes such donor systems are able to generate novel stereochemical, electrochemical and electronic properties. Metal complexes of chelating agents derived from hydrazine-S-methyldithiocarboxylate and its acid amide were widely used as nitrogen-sulphur containing ligands. Thiosemicarbazones possess a wide range of medical properties which have been reported by various workers to be active against tuberculosis, leprosy, bacterial infections, viral infections, psoriasis, rheumatism, trypanosomiasis and coccidiosis. Thiosemicarbazones are very promising molecules in coordination chemistry because of their pharmacological properties [44]. The earliest known antivirals are thiosemicarbazones. The bioactivity of these ligands is due to the inhibition of ribonucleotide reductase and due to complexation with essential metals. Thiosemicarbazone iron derivatives show a wide range of biological properties. It has been proposed that the cytotoxicity and antitumoral activity of these compounds is related, at least in part, to the reaction of thiosemicarbazone. Iron (III) derivatives of pyridine-2-carbaldehyde thiosemicarbazone support the evidence of the reaction with thiols and subsequent formation of iron (II) species. However, up to date there are no crystal structures of iron (II) entities arisen from this process. The first crystal structure of a bis(pyridine-2-carbaldehyde thiosemicarbazone) iron (III) complex was recently reported (Figure 10).

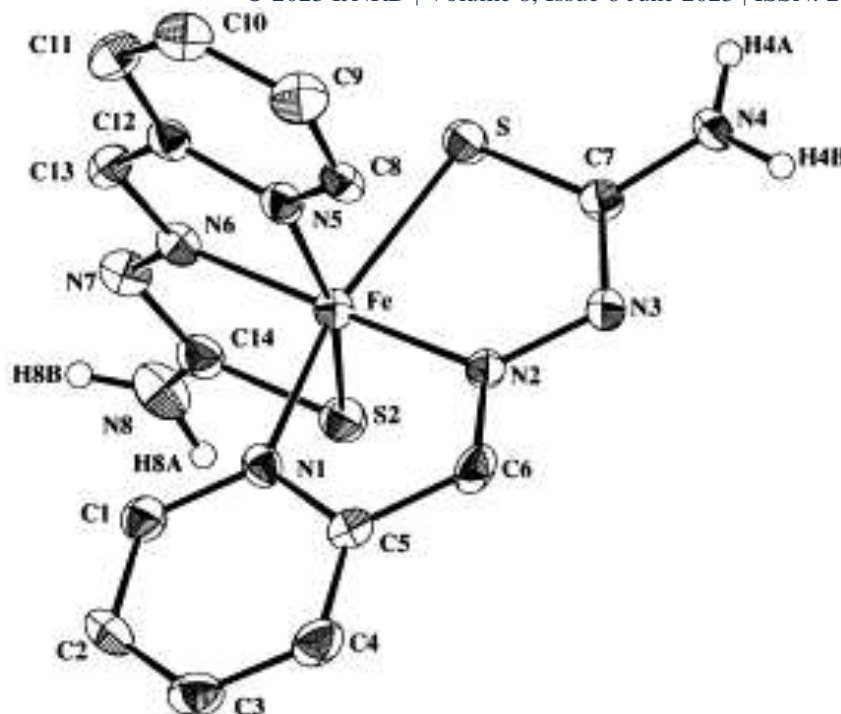
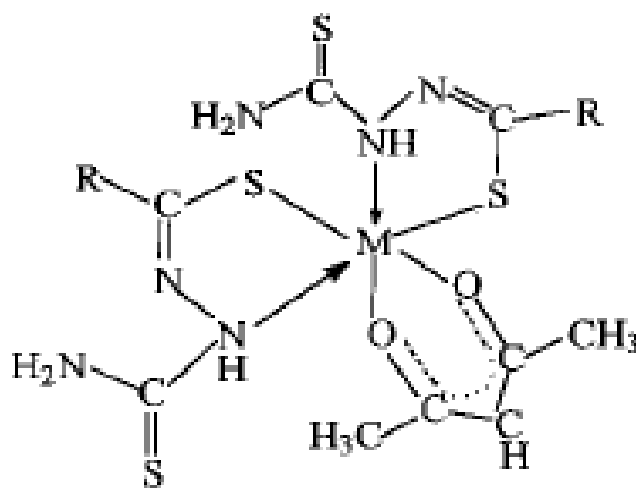


Figure 10: The first crystal structure of a bis(pyridine-2-carbaldehyde thiosemicarbazone) iron (III) complex

Singh and coworkers have synthesized 3d-metal complexes (Figure 11) of this ligand and screened them for their in vitro and in vivo antitumour activity.



b. $[M(Hftsc)_2(acac)]$, (M = Fe or Mn)

Figure 11: Structure of the synthesized ligand

The structural diversity of thiosemicarbazide based compounds is considerably increased not only due to the condensation of the different carbonyls but also due to the alkylation of the different parts of the thiosemicarbazide moiety. While alkylation of nitrogen atoms preserves its usual coordination, through the sulphur and nitrogen atoms, the alkylation of the sulphur atom changes the coordination to the NN mode, characteristic for isothiosemicarbazides. Yildiz *et al.* synthesized bis(imido) unsymmetrical multidentate Schiff base ligands from salicylaldehyde, 5-bromosalicylaldehyde, 5-nitrosalicylaldehyde and naphthaldehyde with thiosemicarbazide and their metal complexes and studied their antimicrobial activity. (Figure 12)

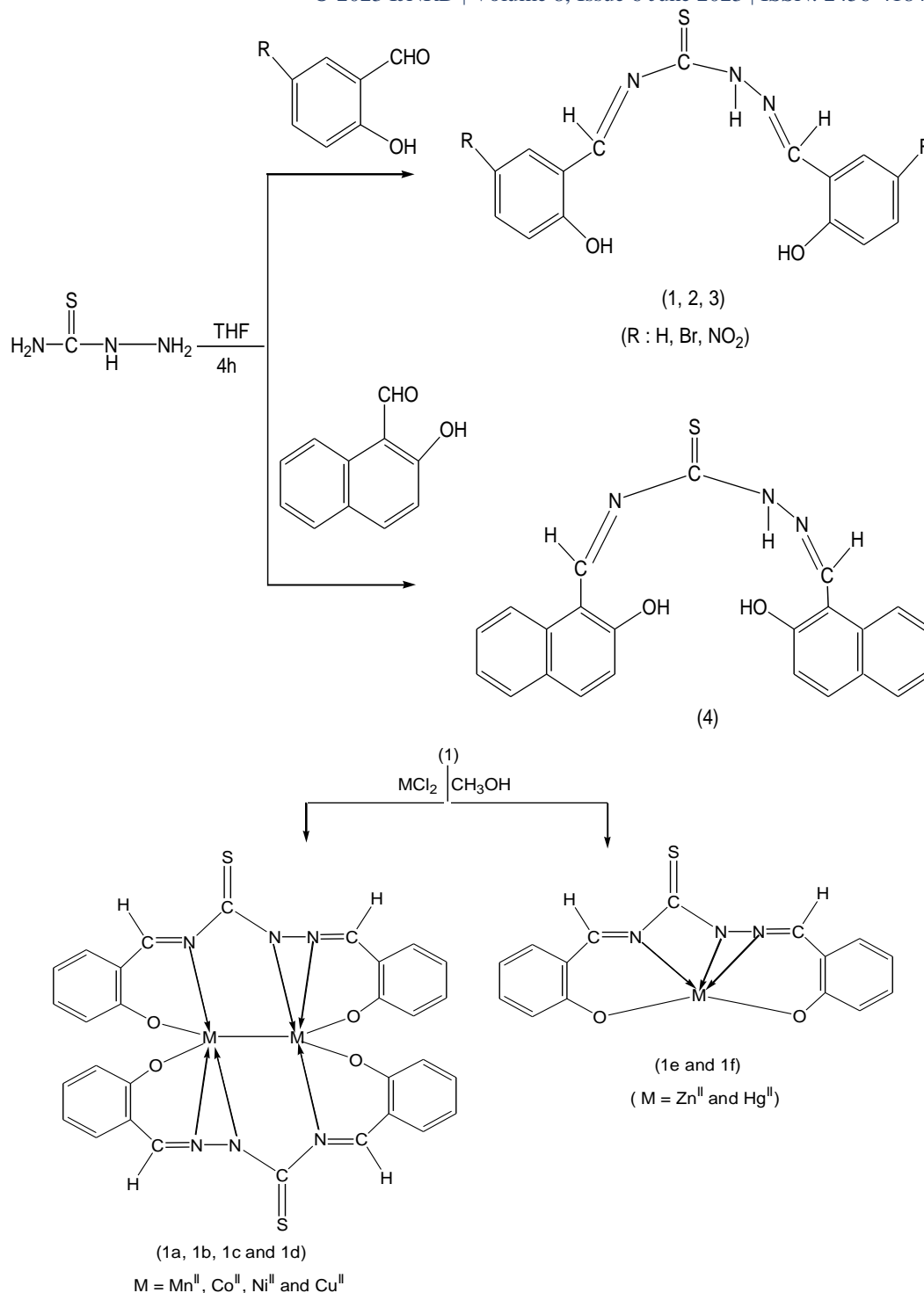


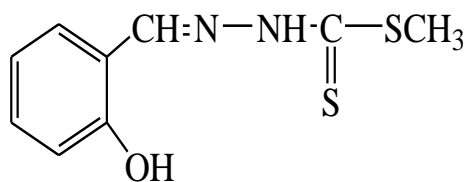
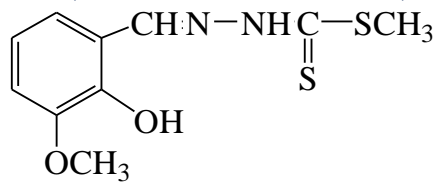
Figure 12: Scheme for Schiff base ligands synthesis

Wilson *et al.* synthesized di-2-pyridyl ketone ⁴N-phenyl thiosemicarbazone and its metal complexes. The ligand and its metal complexes have also been biologically screened to show the effect on cell growth and cell proliferation *in vitro* on *Shewanella oneidensis*. A novel Sn(II) complex from pentadentate ligand bis-(4-N-methylthiosemi-carbazone)-2,6- diacetylpyridine was synthesized electrochemically recently (Figure 13).

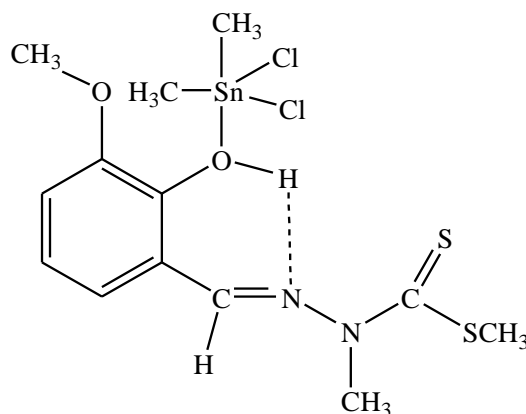
2.3 DITHIOCARBAZATE AND THEIR METAL COMPLEXES

NC(=S)N
$$\begin{array}{c} \text{H} & & \text{H} \\ & \diagdown & / \\ & \text{N} - \text{N} \\ & / & \diagdown \\ \text{H} & & \text{H} \end{array}$$
$$\text{NH}_2-\text{NH}-\text{C} \begin{array}{l} \text{// S} \\ \text{\textbackslash SNH}_2 \end{array}$$
$$\text{NH}_2-\text{NH}-\text{C} \begin{array}{l} \text{//S} \\ \text{\textbackslash SC}_2\text{H}_5 \end{array}$$

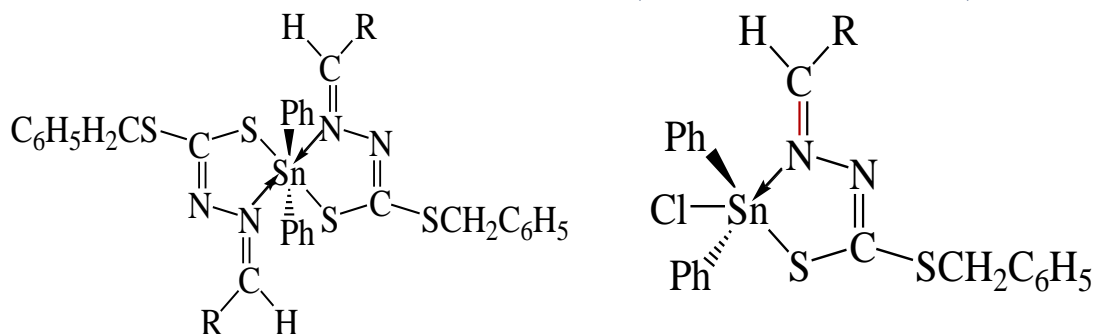
Gopinathan *et al.* here synthesized and characterized organo-titanium (IV), -tin(IV) and lead (IV) complexes with S-methyl- β -N-(2-hydroxy phenyl) methylendithiocarbazate (H_2SMSaD) (Figure 18), S-methyl- β -N-(2-hydroxy-3-methoxy-phenyl) methylendithiocarbazate (H_2SMVD) (Figure 19), 1-(2-hydroxy phenyl)-2,3-diaza-4-methylthio-5-thia-hexa-1,3-diene ($HSSMSa$) and 1-(2-hydroxy-3-methoxy phenyl)-2,3-diene ($HSSMV$).

**Figure 18: H₂SMSaD****Figure 19: H₂SMVD**

Gopinathan *et al.* also synthesized few organotin (IV) complexes with N-methyl-S-methyl-β-N-(2-hydroxy phenyl) methylene dithiocarbazate (HNMSMSaD), N-methyl-S-methyl-β-N(2-hydroxy-1-naphthyl) methylene-dithiocarbazate (HNMSMND) and N-methyl-S-methyl-β-N-(2-hydroxy-3-methoxyphenyl) methylenedithiocarbazate (HNMSMVD) (Figure 20).

**Figure 20: Me₂SnCl₂.HNMSMSa**

Schiff bases derived from S-alkyl / aryl esters of dithiocarbazoic acid have been the subjects of considerable study. The presence of hard N- and soft S-donor atoms in the backbones of these ligands enable them to react readily with both transition and main group metal ions yielding stable metal complexes some of which have been shown to exhibit interesting physico-chemical properties and significant biological activity. Schiff bases derived from S-alkyl / aryl-esters of dithiocarbazoic acid often act as versatile chelating agents and exhibit promising bioactivities. Ali *et al.* synthesized and characterized few transition metal complexes with S-methyldithiocarbazate of isatin. Singh *et al.* synthesized and characterized organotin(IV) complexes with the ligands derived from S-benzoyldithiocarbazate of some heterocyclic aldehydes (Figure 21). These complexes were also reported for their good antibacterial and antifungal activities.



Where, R:

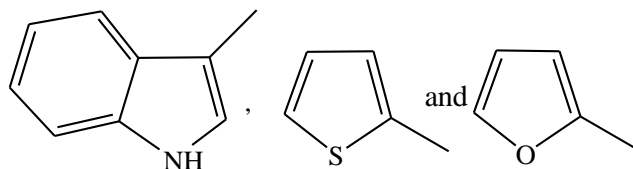


Figure 21

Makode *et al.* synthesized and characterized Schiff base derived from 2-hydroxy-5-chloroacetophenone and S-methyldithiocarbamate and its coordination complexes with various transition metals (Figure 22). The antibacterial activities of the ligand and its complexes have been screened against *E. coli*, *S. aureus*, *Pr. mirabilis* and *S. typhi*.

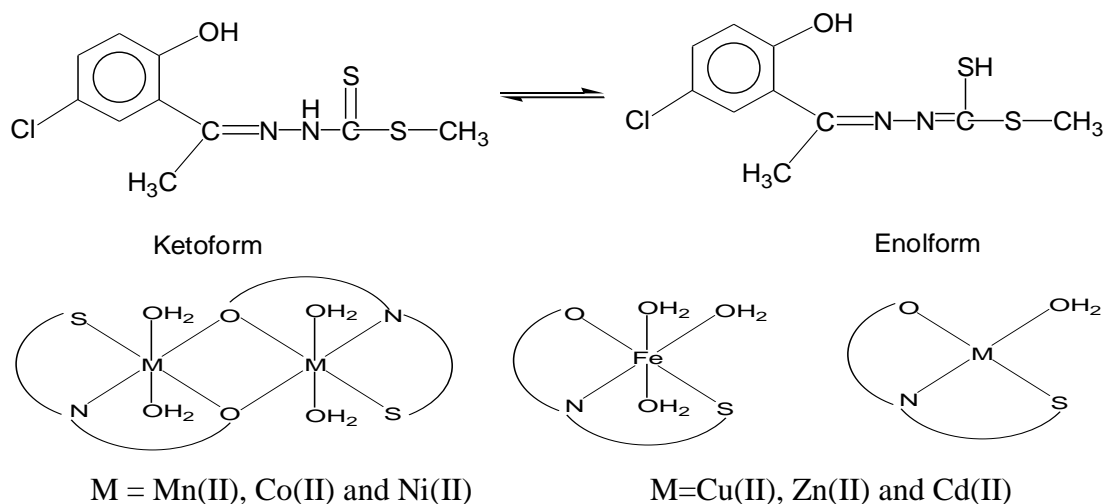


Figure 22

2.4 ISONICOTINOYL HYDRAZONE METAL COMPLEXES

Hydrazones are a versatile class of ligands that have extensive applications in various fields, possessing pronounced biological and pharmaceutical activities as antitumor, antimicrobial [45], antituberculosis and antimalarial agents. Hydrazones play an important role in improving the antitumor selectivity and toxicity profile of antitumor agents by forming drug carrier systems employing suitable carrier proteins. They also have anti-inflammatory and analgesic activity equal or close to that of aspirin. The past few decades have seen the introduction of a number of pharmaceutical compounds which contain five, six, and seven-membered rings such as piperazines, piperidines, imidazoles, benzodiazepines and other heterocycles containing nitrogen, sulphur and oxygen. Systems of this kind play a significant role in many biological processes

due to their coordinating ability to the metal ion. Bioinorganic and biomimetics, containing a C=N bond, are widely represented. Schiff bases have been intensively investigated recently owing to their strong coordination capability and diverse biological activities, such as antibacterial and antitumor activities [46]. The tuberculostatic activity of isonicotinic acid hydrazide and its aroylhydrazones containing azomethine nitrogen is attributed to their ability to form stable complexes with *d*- and *f*-block metal ions [47]. Interest in the study of hydrazones has been growing because of their antimicrobial, antituberculosis and antitumour activity [48]. Isoniazid Schiff bases have been found to show better anticancer and antitubercular activity than isoniazid [49]. The remarkable biological activity of acid hydrazides $R-CO-NH-NH_2$, their corresponding aroylhydrazones $R-CO-NH-N=CH-R$, and the dependence of their mode of chelation with transition metal ions present in the living system have been of significant importance in the past. Chemical modification of the hydrazine unit of isoniazid with a functional group that blocks acetylation, while maintaining strong antimycobacterial action, has the potential to improve clinical outcomes and reduce the emergence in patients of acquired isoniazid resistance. Isoniazid Schiff bases and their metal complexes exhibit good antimicrobial activity than isonicotinic acid hydrazide [50]. The isonicotinoyl hydrazone derivative of some rare earth metals and the crystal structure of the Eu complex were determined by X-ray diffraction analysis. X-ray diffraction analysis showed that the coordination polyhedron of the Eu complex is a tricapped trigonal prism (Figure 23).

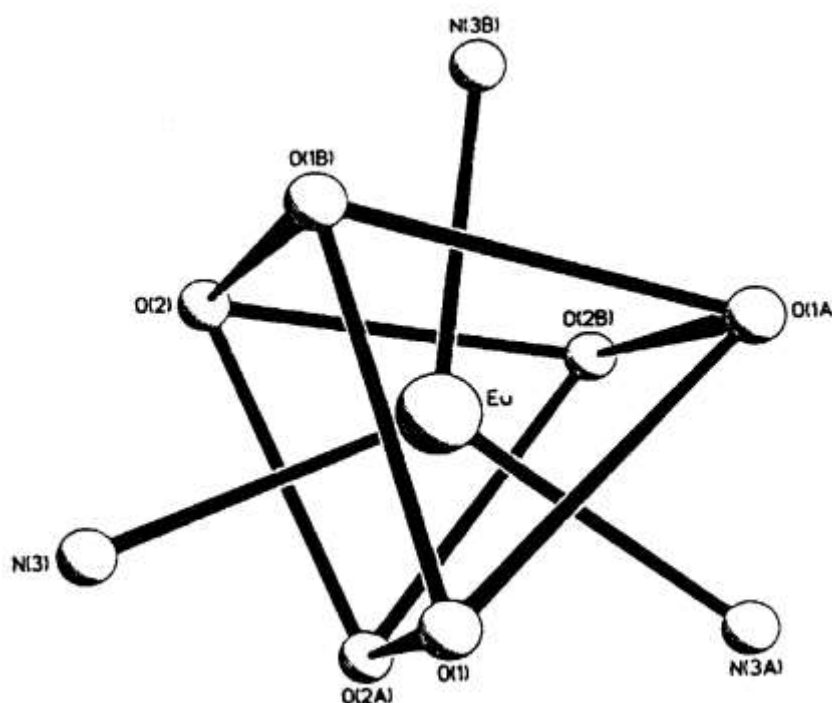


Figure 23: The coordination polyhedron of Eu(III) complex

3. CONCLUSION

A new class of ligand known as Schiff base ligands plays an important role in the development of coordination chemistry. In the recent years the chemistry of Schiff base ligands along with their metal complexes attracted enormous attention of researchers because of their extensive pharmacological

applications. Schiff base ligands and their corresponding metal complexes exhibit good biological activity such as antibacterial, antimicrobial, antioxidant, antiviral, antifertility, and antitumor, antiviral activities. Because of all these biological activities Schiff base metal complexes shows a wide range of applications in medical field. Along with medical applications Schiff base ligands and their metal complexes also shows a wide range of applications in a variety of fields such as catalysis, dyes, and nanotechnology. Schiff base ligands can form stable metal complexes with different moieties like semicarbazones, Isonicotinoyal hydrazone, Dithiocarbazate, and Thiosemicarbazones etc. and exhibits good pharmacological applications.

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