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Metal Complexes of Biological Active 2-Aminothiazole Derived Ligands[1]

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Abstract—The most imperative outcomes of extensive sterdies (synthesis, spectral, structural characterization and biological applications) of metal complexes with thiazole derived ligands are reviewed. A large number of coordination compounds are known but still there is a need of new compounds to develop various efforts in different fields for biomedical applications. The synthesis of Schiff base ligands is very important, and it has recently drawn the attention of numerous research groups, making this area constantly evolve. Authors are also synthesizing some novel biologically potent ligands and their unique complexes and complexes found more biological active agents than that of ligands against bacteria, fungi and herbs. Highlights: Schiff bases and their metal chelates catalyze reactions; Schiff bases derived from sulfane thiadiazole show toxicities against insects; Schiff bases of thiadiazole have good plant regulator activity; Phenyl ring attached to the thiazole group showed interesting structure activity.

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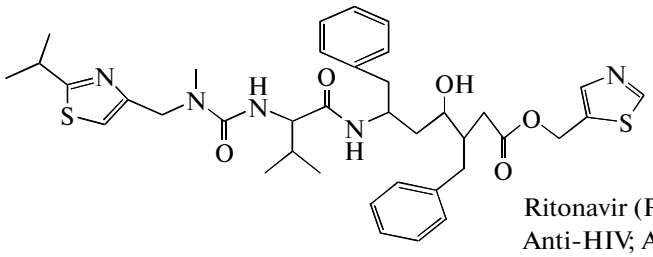
INTRODUCTION

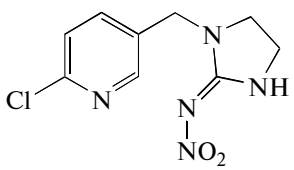
Azomethine (–N=CH–) functional group is characterized as imine group which is important for elucidating the mechanism of transamination and racemization reactions in biological systems and are also known to have biological activities, such as antimicrobial, antifungal, antitumor and herbicidal. They occupy an important position as ligands in metal coordination chemistry, even almost a century or since their discovery.

GENERAL ASPECTS OF THIAZOLE MOIETY

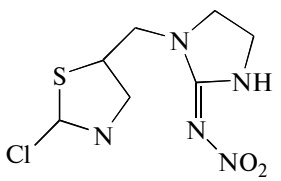
Thiazoles (–N=C–S) containing moiety has been employed as antipsychotic and antibacterial. Thiazole derivatives, particularly amino thiazoles, play vital role in pharmaceutical practice owing to their wide biological activities [1–4] like fungicidal, antimicrobial, anti-tuberculosis, anti-cancer and anti-inflammatory [5, 6]. For example, ritonavir an anti-HIV drug contains a 5-substituted oxymethylthiazole moiety, and an isostere of the important insecticide, imidacloprid has 2-chloro-5-substituted methylthiazole as part of the molecule. Structure of some cited drug molecules are illustrated below:



Ritonavir (Protease Inhibitor; Anti-HIV; Antiviral)



Imidacloprid (Insecticide)



Imidacloprid isostere (Insecticide)

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The substituted thiazoles compounds have a number of characteristic pharmacological features, such as relative stability and ease of starting materials, built in biocidal unit, enhanced lipid solubility with hydrophilicity, easy metabolism of compounds. The first syntheses of the thiazolic ring were made at the end of the nineteenth century when the initial research was carried out by scientists, such as Hantzsch, Hubacher, Traumann, Miolatti, Tcherniac, and Gabriel. The derivatives of pyridine and thiazoles soon constituted an important part of heterocyclic chemistry, as much from the point of view of the initial research as from the practical aspect. Their biological and pharmaceutical interest is in fact important as they appear in the composition of certain vitamins, such as vitamin B_1 (thiamine) and in the penicillin's. Reduced thiazoles serve in the study of polypeptides and proteins and occur as structural units in compounds of biological significance, for example, firefly luciferins and in antibiotics bacitracin-A and thiostrepton. Equally, some derivatives of the 2-aminothiazoles are used as fungicides, pesticides, and bacteriocides, and others possess mitodepressive and mitostatic properties, and a large range of 2-amino (and hydrazino)5-nitrothiazoles (nitridazole) are devoid of schistosomicidal activity. Certain Schiff bases derived from 2-amino-5-phenylthiazole and their reduction products show diuretic properties. Others such as rhodanines are used as intermediates in the synthesis of amino acids, peptides, and purines. In industry, several mercaptothiazole derivatives serve to accelerate the vulcanization of rubber, and alkyl- and acylthiazoles are known to be interesting flavoring agents. Finally, derivatives of thiazole are also to be found in certain natural products: a new amino acid incorporating the thiazole ring has been recently isolated from the fungus *Xerocomus subtomentosus*. Syntheses of thiazoles have been carefully reviewed by Wiley et al., and in 1957 the subject was dealt with in an excellent survey by Sprague and Land. This list was usefully supplemented in 1970, 1973, and 1975 by the publications of Kurzer, and a number of books on penicillin contain much information on the reduced thiazole system. Asinger and Offermanns have reviewed the chemistry of d^3-thiazolines, and Ohta and Kato's comprehensive survey on sydnones includes a section of mesoionic thiazoles.

It is well-known that the thiazolyl group is of great importance in biological systems [6]. Alkyl/arylaminoacetyl derivatives of 2-amino-4-phenylthiazolyl [7], 2-aminobenzothiazolyl [8], 2-amino(substituted)-benzothiazolyl [9], 2-phenylamino-4-phenylthiazolyl [10], 2-amino-4-methylthiazolyl [11] as well as 3-aminobenzo[*d*]isothiazole derivatives [12] were found to have a potent local anesthetic activity, anti-inflammatory, analgesic, and antipyretic activity [13, 14]. Thiazoles and Schiff bases are of great importance for the preparation of various pharmaceuticals and are used in many other areas of chemistry as starting materials [15, 16]. 2-Aminothiazoles are known mainly as biologically active compounds with a broad range of activity and as intermediates in the synthesis of antibiotics and dyes [6]. Substituted α-halo ketones, like those used in the production of our ligand, are used for different purposes, especially in the synthesis of heterocyclic substances [17–21]. Much research have been devoted [22–30] to study the metallo-organic and biological behavior of such derivatives containing the (CH=N) azomethine linkage. The biological activity of these compounds may be connected to their ability [31, 32] to form complexes with certain metal ions which may lead to a "locked geometry" via coordination mechanism so that only certain substances are able to become attached to the framework of this interaction [33, 34]. Multidentate ligands are extensively used in coordination chemistry, since they can be applied in the construction of new frameworks with interesting properties [35]. Among these ligands, the linear or cyclic Schiff bases have attracted much attention since most of their compounds prepared to date exhibit noteworthy bioactivity and desirable or predictable physicochemical, stereochemical, electrochemical, structural properties, etc. [36, 37]. These properties are due not only to the diverse condensation products of the amine-aldehyde reaction, but also to the participation of the specific metal atom and ligands. In some cases, the structural and biological properties of the corresponding coordination compounds are more noteworthy than those of the ligands alone. Their use as tools for the analysis of pharmacological [38, 39] substances and as analgesic, anti-inflammatory, antibiotic, antimicrobial [40] and especially as anticancer [41] agents are well known. Transition metal complexes of Schiff bases have received considerable attention, mainly due to their preparative accessibility, structural diversity, and wide range of applications in various fields [42–44]. Among these ligands, thiazole and its derivatives have been well studied owing to their significant activities [45–48]. Recognition of thiazole and its derivatives in vitamin B and coenzyme carboxylase have generated increasing interest in their structural and functional properties and have created an exciting topic for research [49, 50]. Schiff bases derived from substituted heterocyclic compounds containing nitrogen, sulphur and/or oxygen as ligand atoms are of interest as simple structural models of more complicated biological systems [51–53]. Various heterocycles, especially thiazoles, occupy an important place owing to their versatile bioactivities due to the presence of multifunctional groups [54–57]. Thiazole and its derivatives play significant part in the animal kingdom. Vitamin B1, penicillin and coenzyme cocarboxylase contain the thiazole ring. Polyfunctional ligands based on benzazoles are relevant due to their biological activities [58, 59]. Thiazole derivatives are widely used in the synthesis of the medicinal products, such as sulphathiazole (antibiotic) [60]. Benzothiazoles are used for production of dyes with photosensitizing properties [61]. Also, metal

complexes of Schiff bases with heterocyclic compounds find applications as potential drugs [62, 63].

COORDINATION BEHAVIOR OF THIAZOLE

Thiazole, C_3H_3NS, first described by Hantzsch and Weber in 1887 (Arthur Rudolf Hantzsch (1857–1935) is among the lengthy list of important late 19th and early 20th century German chemists. Besides his synthesis of thiazole, his name has been attached to a pyridine synthesis, and to a pyrrole synthesis. The Hantzsch thiazole synthesis is still important, today is a five-membered aromatic heterocyclic (contains non-carbon atoms in the ring) organic compound that is useful in the manufacture of pesticides, drugs, dyes and other compounds. Some of them exhibit anti-tumor and anti-viral properties. Two modes of coordination must be considered for the system, bonding through nitrogen and sulphur donors. The majority of Schiff bases of 2-aminothiazole derivatives are obtained in good yield by condensation of aqueous and alcoholic solution. Since 2-aminothiazole has an additional potential coordination site in the amino nitrogen, it was considered worthwhile to study the complexes of this ligand.

EVOLUTION OF CONCEPT

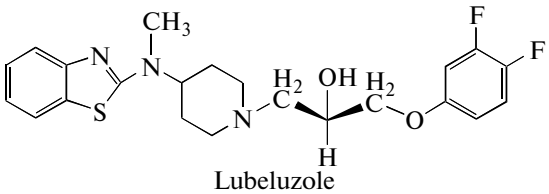
Earlier, research work was focused on the synthesis, characterization and biological studies of coordination compounds with Schiff bases [5] of polyamines with heterocyclic aldehydes as ligands due to its coordinative conformational and physiochemical properties, while later in order to mimic biological systems and mechanisms in the process of drug design [6]. The five or six membered chelate ring Schiff bases stabilize, in thermodynamic terms of entropy, the compounds synthesized. The main aim behind introducing chelate ring was to improve the biological activity of some of the already studied compounds [64] through the synthesis and study of novel Schiff base mixed-ligand coordination compounds, by the insertion of biological molecules such as thiazoles, into the coordination sphere. The bioactivity of S, Thiazoles is largely due to their structural similarities with proteins imidazolyl entities [65] as well as biological, structural, electronic and spectroscopic features [66, 67]. Their participation in the formation of compounds can modify [68, 69] the bioactive and pharmaceutical characteristics of adducts, a recent example being the report of the effect of chelation on the bactericidal properties of thiazole-derived compounds [70, 71]. Among the thiazoles employed, the 2-amino-5-methylthiazole is most appropriate for the enhancement of the bioactivity of already synthesized compounds. This unique characteristic of the 2-amino-5-methylthiazole molecule could be attributed to its electronic distribution resulting from the $+I$ effect of the lipophilic methyl, the $+R$ effect of the hydrophilic amino group and the $-R$ effect of the thiazole ring. Furthermore, the position of the methyl group on the fifth carbon atom is essential due to steric reasons, since the 2-amino-5-methylthiazole molecule where the methyl group is located on the fourth carbon atom, does not exhibit activity. 2-Amino-5-methylthiazole Cu complexes have shown interesting results against cancer cell lines. Interestingly, this compound seems to have a high activity against epithelial cancer cell lines like T47D (breast cancer), HT29 (colon cancer) and HeLa cells (squamous carcinoma of the cervix), showing a less significant activity against the L929 normal fibroblastic cell line [64].

SCOPE OF THIAZOLE DERIVED LIGANDS

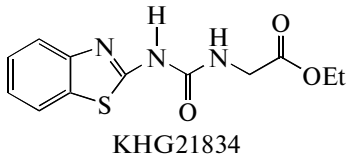
Parkinson's disease (PD) is the most common neurodegenerative movement disorder, characterized by a specific loss of dopaminergic neurons in the substantia nigra pars compacta and affecting the population above the age of 60 years [72]. The major clinical symptoms of PD include bradykinesia, postural instability, rigidity and tremor. Furthermore, a number of patients also suffer from anxiety, depression, autonomic disturbances, and dementia. The underlying cause of this selective cell death is not understood pharmacological therapy of PD is presently aimed at symptomatic control because clinically effective neuroprotectants capable of slowing the progression of nigral dopaminergic neuron degeneration are yet to be identified. An alternative approach to the treatment of this disorder would be the use of neuroprotective or antioxidant therapy to prevent or slow down the degeneration of these neurons. For many years, thiazole derivatives have been the subject of most structural and medicinal studies because of their biological potential. They are of interest as potential neuroprotective agents [73] as well as the possible core skeletons of adenosine receptor antagonists with moderate affinity and selectivity at the A_{2A} receptor site [74]. Benzothiazoles are highly interesting molecules for drug development, because they are known to be useful for treating neurodegenerative disorders [75]. Among the most efficient compounds, lubeluzole has been shown experimentally to preserve neurological function and reduce infarct volume in animal models of focal brain ischemia [76], while other derivatives, such as KHG21834 were capable of protecting PC12 cells and cortical and mesencephalic neurons from amyloid b-induced degeneration [77].

In addition, riluzole, a Na^+ channel blocker with antiglutamatergic activity, is effective against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurodegeneration of the nigrostriatal dopaminergic neuronal pathway and contains a benzothiazole ring [78]. Moreover, riluzole prolongs survival and delays muscle strength deterioration in mice with progressive motor neuropathy [79] and shows neuroprotection in gerbil model of transient global ischemia [80]. Also, some fused benzothiazoles [81] and amino-

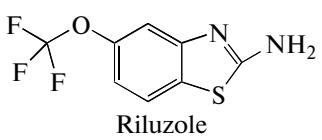
benzothiazole derivatives [82] are reported to be useful for the therapeutic or prophylactic treatment of humans suffering from ageing of, or degenerative diseases of the nervous system which are associated with oxidative stress. A series of urea substituted benzothiazoles are said to be effective in controlling or prevention of PD [83, 84] In previous work, a series of naphtha[1,2-d]thiazol-2-amine derivatives were found to act by reducing the formation of MDA and increasing the formation of SOD and GSH-Px in mice brain, suggesting their neuroprotective properties [85]. In addition, the study of naphthalene derivatives has become of much interest in recent years on account of their antioxidant and antiparkinsonian activities. Their antagonistic role against l-glutamate-mediated excitotoxicity in the central nervous system has been documented. Structure of some cited molecules are illustrated below:



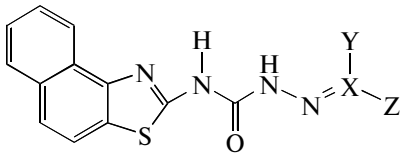
Lubeluzole



KHG21834



Riluzole

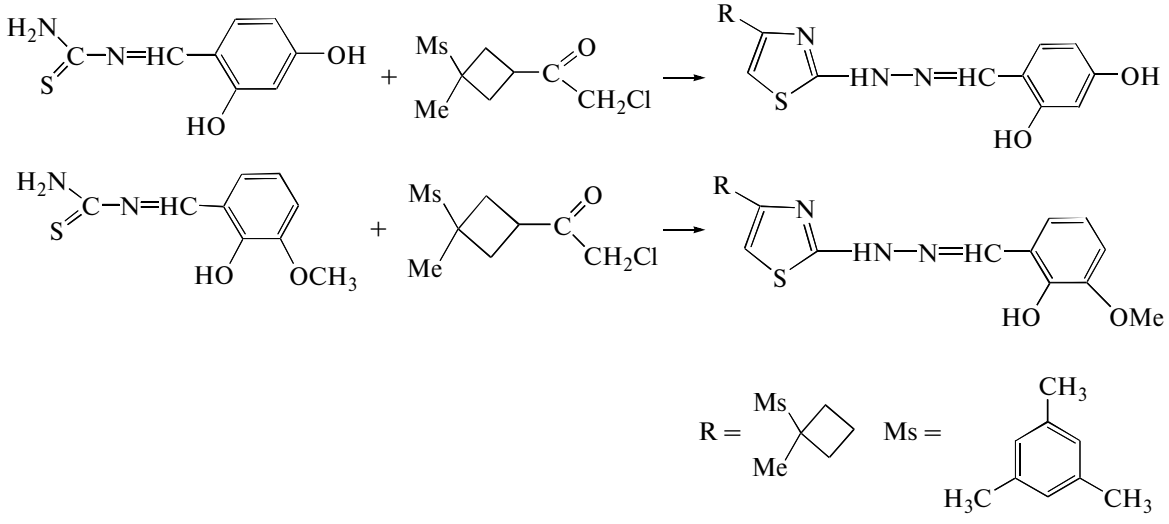


Naphthal[1,2-d]thiazole-2-amine derivatives

Many anticancer and anti-bacterial drugs are known to behaves as versatile ligands [86] some of which exhibit increased anticancer activity when administered in the complex form with the metal ions [87, 88]. It has been suggested [89] that certain type of cancers are caused by viruses. The interaction between metal ion and their ligands with cancer associated viruses might represent an important route in designing [90] new anticancer therapies for tumors that becomes resistant to the conventional drugs. A recent methodology to design novel antiviral therapies is achieved by coordinating a metal ion from an important biomolecule, for instance a zinc finger protein with antiviral agent, usually containing sulphur functionalities with good complexing behavior. All these observations have attracted our attention to report antibacterial thiazole derived Schiff bases [91].

COMPLEXATION OF THIAZOLE

Synthesis of symmetrical bis Schiff bases with a series of aromatic aldehyde derivatives under solvent free conditions at elevated temperature and structure of thiazole derived ligands are given below:

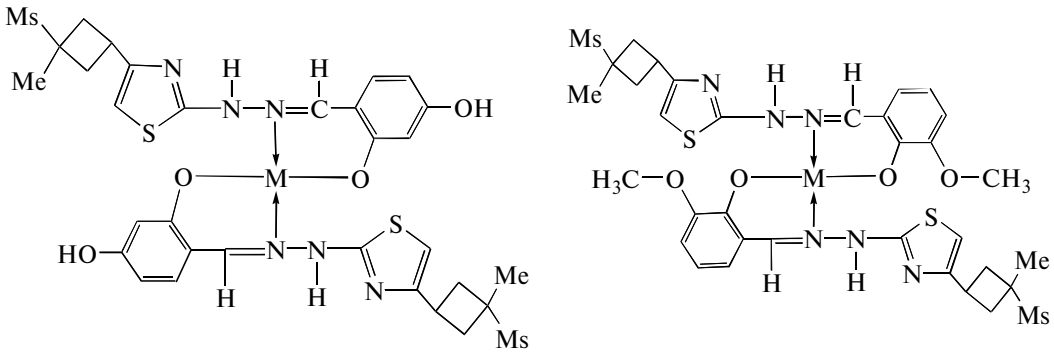


Aromatic aldehydes with substituents carrying either electron donating or electron withdrawing groups reacted successfully and gave products in good yields [92].

Fe(III) coordination compounds with 2-aminobenzothiazole have been prepared and identified as $(C_6H_4NHC(NH_2)S)_2[FeCl_4]Cl(H_2O)$ and $(C_6H_4NHC(NH_2)S)_3[Fe(C_2O_4)_3](H_2O)_2$. The compounds were characterized by thermo gravimetric analysis in conjunction with evolved gases in air and spectroscopic studies. On the basis of quantum mechanical calculations shows evidence that $(C_6H_4NHC(NH_2)S)_2[FeCl_4]Cl(H_2O)$ can be classified as anion–π interactions. The interaction between non-coordinated chloride ion and 2-aminobenzothiazolium cations is characterized by long distances with strength typical for ion-pair interactions and the directionality characteristic for anion–π interactions. Although the existence of anion–π interactions is questionable [93], in the present case the results of quantum-mechanical calculations indicate that the chloride ion and thiazolium ring are connected not only by electrostatic interaction but also by bonding interaction, which can be considered as anion–π contact. Since protonation is a common process occurring in physiological systems and almost all drugs or bioactive molecules undergo protonation before they enter the reaction chain, the effect of non-covalent interactions such as ion-pairing and anion–π interactions can be important and might help to design anion receptors [94–96].

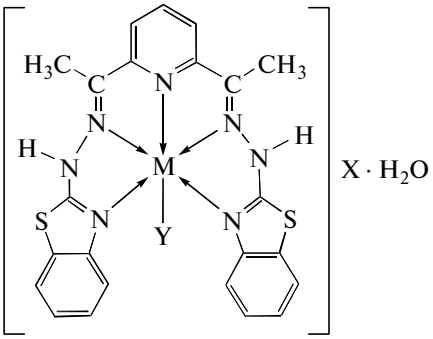
Interaction of bidentate ligands L–L (L–L = 2-(2'pyridyl)-benzimidazole (PBI), 2-pyrazinecarboxylic acid (PC), and 2-pyrazinecarboxamide (PCA)) with $[PdCl_4]^{2-}$ resulted in immediate precipitation of the mono-substituted derivative $[Pd(L–L)Cl_2]$. The PBI derivative was crystallized with three water molecules, the PC derivative isolated with five H_2O, while the PCA species separated with two H_2O molecules. The binuclear palladium complexes $[Pd(L)Cl_2]_2$ (L = 2-aminothiazole (AT) or 2-aminobenzimidazole (ABI)) were obtained from reactions of ethanolic solutions of $[PdCl_4]^{2-}$ with L at elevated temperature. Both complexes crystallized with a water molecule/mol. of compound as determined from TG analysis [97].

Copper(II) complexes $[Cu(L^1$ or L^2 or $L^3)(PPh_3)_2(N_3)_2]$ and $[Cu(L^1$ or L^2 or $L^3)(PPh_3)_2(NCS)_2]$ (L^1 = 4-(4'-phenyl,2'-thiazolylazo)chlorobenzene, L^2 = 4-(4'-phenyl,2'-thiazolylazo)bromobenzene, and L^3 = 4-(4'-phenyl,2'-thiazolylazo)iodobenzene) have been prepared and characterized on the basis of microanalytical data. The electrochemical behavior of the complexes showed that the redox responses of Cu(II) complexes shifted to more negative potential with decrease in electron-withdrawing substituents on the azo ligands. Complexes exhibit blue-green emission with high-quantum yield [98]. Suggested structures of such complexes are illustrated below:



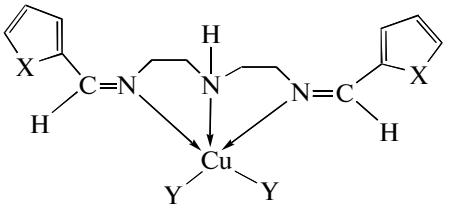
M = Co(II), Cu(II), Ni(II), and Zn(II)

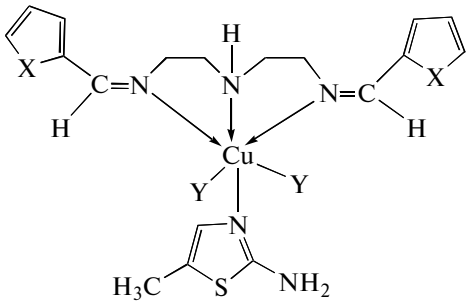
Proposed structure of metal(II) complexes with ligands containing different and important functionalities cyclobutane, thiazole and Schiff base characters are shown below:



M = Co(II), Cu(II), Ni(II), Zn(II), Mn(II), and Cd(II) (Y = Cl, X = Cl^-) and V(IV) (Y = O, X = SO_4^{2-}).

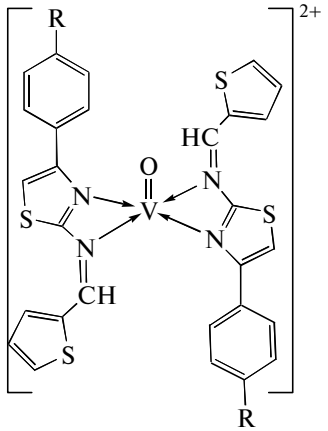
The extensive synthetic possibilities of these heterocycles, due to the presence of several reaction sites, hold promise for the preparation of new thiazole derivatives, i.e. 4-(1-methyl-1-mesitylcyclobutane-3-yl)-2-(2,4-dihydroxybenzylidene hydrazino) thiazole and 4-(1-methyl-1-mesitylcyclobutane-3-yl)-2-(2-hydroxy-3-methoxybenzylidenehydrazino) thiazole and their mononuclear complexes with acetate salts of Co(II), Cu(II), Ni(II) and Zn(II) in ethanol have been prepared. Proposed structures of Cu complexes X = O, S and Y = Cl, Br, and NO_3 are the following:





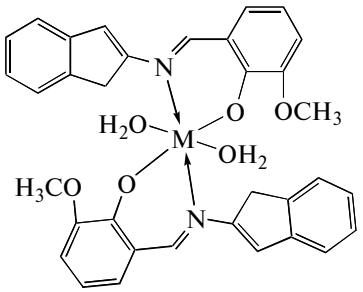
These are very soluble in organic solvents such as Et_2O and benzene. These are not stable for long under laboratory conditions and are highly affected by direct sunlight, decomposing over two months. Hence, they are being used as prepared, without delay. More hot solutions were used for complexation. Crystallization attempts of ligands and complexes in different solvents failed and stable at room temperature [99].

Chelating properties of 2,6-diacetylpyridinebis-(hydrazone) [6] have been investigated and found that adopts octahedral and pentagonal bipyramidal geometry on coordination with transition metal ions. However, the nature of coordination depends also on the metal ion, pH of the medium, reaction conditions, and also the nature of ligands. Cu(II), Co(II), Ni(II), Mg(II), Zn(II), Cd(II), and oxovanadium(IV) complexes were prepared by refluxing the hydrated metal chlorides/sulphate in EtOH with 2,6-diacetylpyridine bis-(2-hydrazinobenzthiazole) acts as pentadentate ligand by coordinating through NNNNN fashion forms octahedral complexes. Thus, colored complexes obtained are insoluble in most organic solvents but soluble in DMF and DMSO. These complexes decompose without melting, when heated above 300°C. Proposed structures of these complexes are given below [100]:

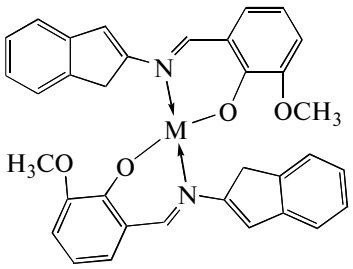


R = H, OH, OCH_3, NO_2, Cl, Br, CH_3

Reaction of diethylenetriamine with 2-thiophenecarbaoxaldehyde or 2-furaldehyde in 1 : 2 molar ratios yield Schiff base which further reacts with the Cu(II) chloride dehydrate, Cu(II) bromide, and Cu(II) nitrate trihydrate to give the corresponding Cu(II) Schiff base compounds. Further, reactions with 2-amino-5-methylthiazole were performed in 1 : 1 molar ratios and yielded monomeric octahedral compounds. General reactions are given in [101]. These novel Schiff base Cu(II) compounds and their adducts with 2-amino-5-methylthiazole are stable, blue or green colored crystals or crystalline powder. Structure of metal Schiff base complexes are the following:



M = Mn(II), Ni(II), Co(II)

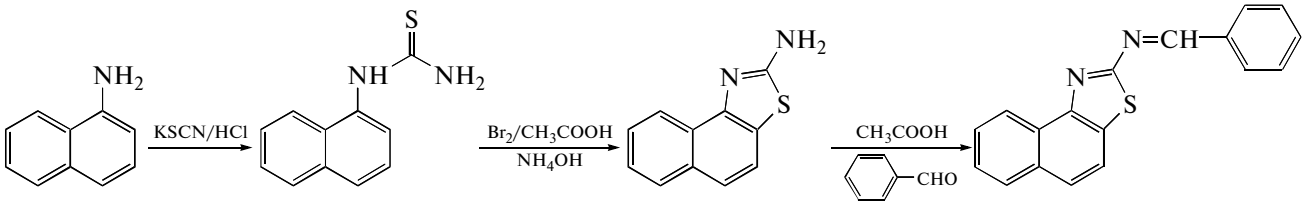


M = Co(II), Zn(II)

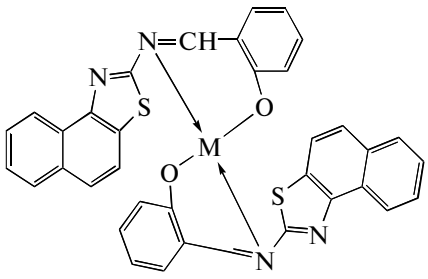
The Schiff base diethylenetriamine is bonded in tridentate fashion through the three nitrogen atoms from Schiff base of diethylenetriamine (dien) with heterocyclic aldehydes and the coordination sphere of the copper is completed by the endocyclic three N from 2-amino-5-methylthiazole and by two Cl^-, or Br^-, or NO_3^- groups in a distorted octahedral geometry. Biological activities, i.e. antiprofilative and antibacterial studies, show that adducts exhibit higher bioactivity compared to the starting materials and 2-amino-5-methylthiazole itself. This means the insertion of 2-amino-5-methylthiazole affects the aggregation of electronic, physiochemical and steric properties of the resulting compounds thus moderating their biological activates. Among transition metal complexes, vanadium is versatile in forming complexes with relevant biological properties and possesses a number of stable and accessible oxidation states. It has been observed that there is a series of nitrogenase metalloenzymes that have vanadium at their active sites. Apart from this insulin mimetic property of vanadium(IV) compounds has stimulated further interest into vanadium complexes. Chemistry of oxovanadium complexes has received less attention so far, and most part of biochemistry of oxovanadium complexes remains obscure. Oxovanadium(IV) complexes of Schiff base 2-amino-4-phenyl thiazole substituted can be represented as follows [102]:

$$VOSO_4 \cdot XH_2O + 2L \xrightarrow{\text{methanol}} [VOL_2]SO_4 + XH_2O.$$

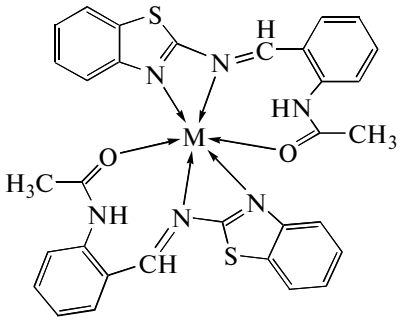
Synthesis of ligand L is given below:



Supposed structure of metal complexes M = Co(II), Ni(II), Cu(II) (reproduced with permission) are the following:



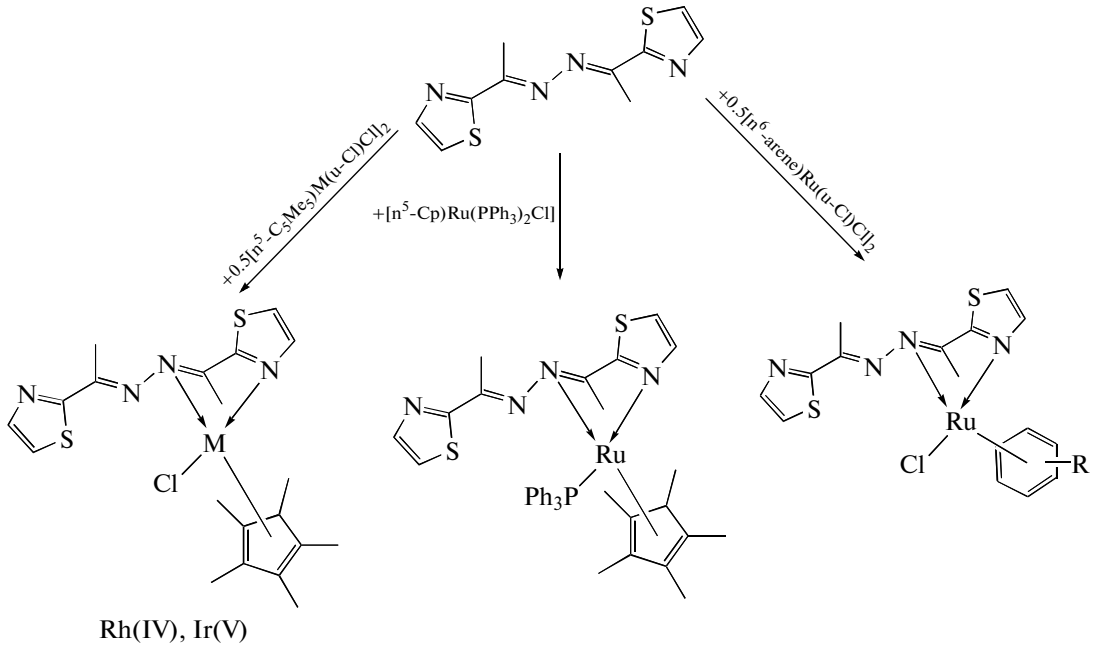
Resulted complexes are sparingly soluble in common organic solvents and show good solubility in DMSO. All of these complexes decompose above 250°C. Schiff bases derived from O-vanillin and 2-aminobenzthiazole acts as monobasic binds the metal atom in bidentate manner via phenolic oxygen and azomethine nitrogen atom. Spectral and thermo gravimetric studies suggest the octahedral structure of Co(II), Ni(II), and Mg(II) with two water molecules in coordination sphere:



Based on the vibrational, electronic and EPR studies a distorted tetrahedral geometry has been proposed for copper complexes. ^1H NMR study reveals tetrahedral

structure of Zn(II) complex. Well defined crystalline homogenous nature of metal complexes is observed from XRD and SEM analysis. Efforts are going on to get single crystal of these complexes [103].

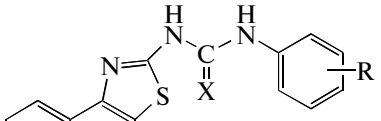
2-Benzylideneaminonapthothiazoles were designed and synthesized incorporating lipophilic naphthalene ring to render them more capable of penetrating various biomembranes. Substituted Schiff bases of naphtho[1,2-d]thiazole-2-amine and metal complexes of 2-(2'-hydroxy) benzylideneamino napthothiazole with Co(II), Ni(II), and Cu(II). Scheme showing syntheses of complexes are the following:



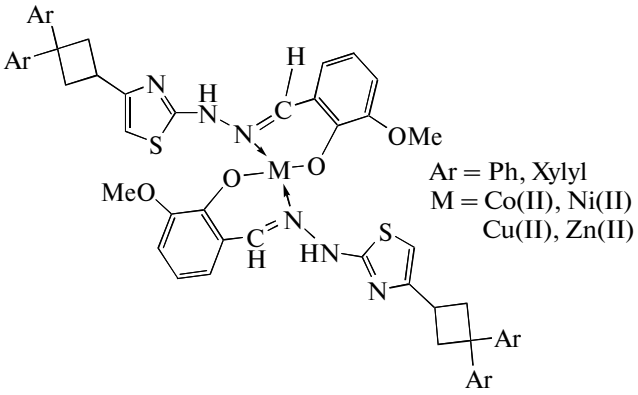
Rh(IV), Ir(V)

These compounds exhibited reasonable antibacterial activity as compared to standard drugs. The results validate the hypothesis that Schiff bases having substitutions with halogens, hydroxyl group and nitro group at phenyl ring are required for antibacterial activity while methoxy groups at different positions in aromatic ring has minimal role in inhibitory activity. Among this of 2-(2'-hydroxy) benzylideneamino napthothiazole showed maximum inhibitory activity and among metal complexes Cu(II) metal complex was found to be most potent [104].

2-Acetamidobenzaldehyde reacts with 2-aminobenzothiazole and its substituted 4-methyl, 4-methoxy, 4-chloro, 4-nitro, and 6-(methylsulfonyl)benzothiazole. These used for the complexation reactions with Co^{2+} and Ni^{2+} metal ions. All the newly synthesized metal complexes were air and moisture stable. They are prepared by the stoichiometric reactions of the corresponding metal(II) salts and the Schiff-bases in the molar ratio of 1 : 2 complexes are amorphous solids, which decompose over 200°C; they are insoluble in common organic solvents, such as ethanol, methanol, chloroform, acetone but soluble in DMSO and DMF [105]. Proposed structure of urea and thiourea derivatives are the following:



Half sandwich platinum group metal complexes with symmetrical Schiff bases come from the fact they can serves as synthetic models related to the biological systems. Mononuclear cationic arene ruthenium complexes having 2-acetylthiazole azine (Ata) ligand, i.e. $[(\eta^6\text{-}C_6H_6)Ru(Ata)Cl]PF_6$, $[(\eta^6\text{-p-}^i prC_6H_4Me)Ru(Ata)Cl]PF_6$, and $[\eta^6\text{-}C_6Me_6)Ru(Ata)Cl]PF_6$ have been expediently prepared. Suggested structures of these complexes are:

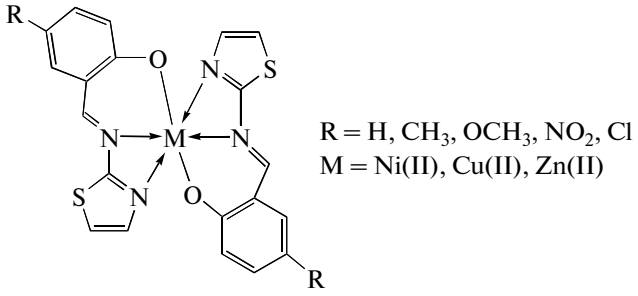


In order to prepare binuclear complexes we have used two fold metal to ligand or one fold metal to mononuclear complexes concentration, but not fruitful in either of the cases. This could be due to the steric strain from arene or pentamethylicyclopentadienyl ligands already present on metal atoms [106].

Thiazole and benzothiazoles carrying a benzenesulfonamide moiety at 2 position of the heterocyclic nucleus have effective antibacterial properties [107]. Synergistic inhibitory activity occurs when the active antibacterial sulfonamidesare tested in combination with trimethoprim against both *Bacillus subtilis* and *Staphylococcus aureus*.

Spiro compounds of benzthiazole, i.e. 3'*H*-spiro[indol-3,2'-[1,3]benzthiazole-2(*1H*)-one] and these ligands possess different centers for coordination with chromium, molybdenum or tungsten. Synthesized Spiro compound show better activity for *E. coli* than isatin. Also chromium complex shows higher inhibition activity than of isatin. Molybdenum and tungsten exhibit a lower activity than the ligand [108].

Series of *N*-(substituted phenyl)-*N*'-(naphtha[1,2-d]thiazol-2-yl)urea and thiourea derivatives were synthesized. The newly synthesized compounds were found to possess antiparkinsonian and antioxidant activities. Antiparkinsonian activity was evaluated on haloperidol-induced catalepsy in mice by employing the standard bar test. All of the synthesized compounds ameliorated the catalepsy induced by haloperidol in mice. The most potent compounds were selected for biochemical evaluation from the brain homogenate. Proposed structures of these complexes are:



These compouds are effective in decreasing the elevated levels of malondialdehydewhile restoring the cellular defense mechanisms, such as glutathione content as well as glutathione peroxidase and superoxide dismutase activities in haloperidol-treatedmice, suggesting the role of free radicals in the pathophysiology of haloperidolinducedcatalepsy and possible antioxidant action of title compounds [109].

Schiff base type starch chelating agent dialdehyde aminothiazole (DASAT) was prepared by reacting dialdehyde starch with aminothiazole. The adsorption between Cu^{2+} ion and dialdehyde aminothiazole starches (DASATs) is found to be dependent on the pH of the solution, the initial concentration of Cu^{2+} ion, as well as the adsorption temperature. The adsorption follows the Langmuir isotherm. The adsorption capacity increases with the increasing DS of the DASAT, and reaches 0.44, 0.69, and 0.95 mmol/g at 20°C, respectively, for DASAT1, DASAT2, and DASAT3. The adsorption process of DASAT3 is endothermic, and the apparent enthalpy is 11.41 kJ/mol. For effectual metal removal, the metal solution should be in a bearable neutral pH range. By raising the DS of the DASAT, the metal removal could reach the level required for distinguished adsorption capacity; thus, DASAT gave a potential application as a low-cost and effective absorbent [110].

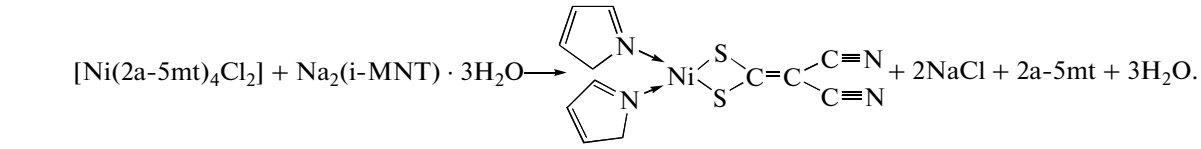
The syntheses, structures and magnetic properties of novel bithiazole based polymeric complexes incorporating ferroions and hexacyanoferrate groups. The polymer referred to as SDP is a condensed product, which obtained from the polycondensation of salicylic acid with 2,2'-diamino-4,4'-bithiazole (DABT) and paraformaldehyde. Its ferro-complex (SDP-Fe^{2+}) reacted with potassiumferricyanide $K_3[Fe(CN)_6]$ in DMSO producing the polymeric–inorganic complex (SDP-Prussian blue). On the basis of preliminary characterization via spectroscopy techniques, reasonable structures have been proposed for these dithiazole based metallopolymers. Studies indicate different magnetic behaviors for both complexes: SDP-Fe^{2+} is antiferromagnetic while SDP-Prussian blue displays characteristics of a soft ferromagnet. The presence of ferromagnetic coupling between iron ions through cyano bridging linkage in SDP-Prussian blue is proposed based on the ESR spectroscopy [111].

Schiff base ligands containing 2,4-disubstituted thiazoles and cyclobutane rings, 4-(1-methyl-1-phenylcyclobutane-3-yl)-2-(2-hydroxy-3-methoxybenzylidene hydrazino)thiazole, 4-(1-methyl-1-*p*-xylylcyclobutane-3-yl)-2-(2-hydroxy-3-methoxybenzylidene-hydrazino) thiazole, and their mononuclear complexes with a 1 : 2 metal–ligand ratio have been prepared from acetate salts of Co(II), Cu(II), Ni(II), and Zn(II) in EtOH [112]. The structures of these complexes look like the structures of ruthenium complexes having 2-acetylthiazole azine ligand. The authenticity of the ligands and their complexes has been established by microanalyses. Thermal properties of the ligands and complexes have been studied by TGA and DSC techniques. Antimicrobial activities of the ligands and their complexes were found to be active against some of the microorganisms studied.

Thiazole derived tridentate Schiff-bases and its metal chelates of the type $[M(L_2)X$ (M = Ni(II),

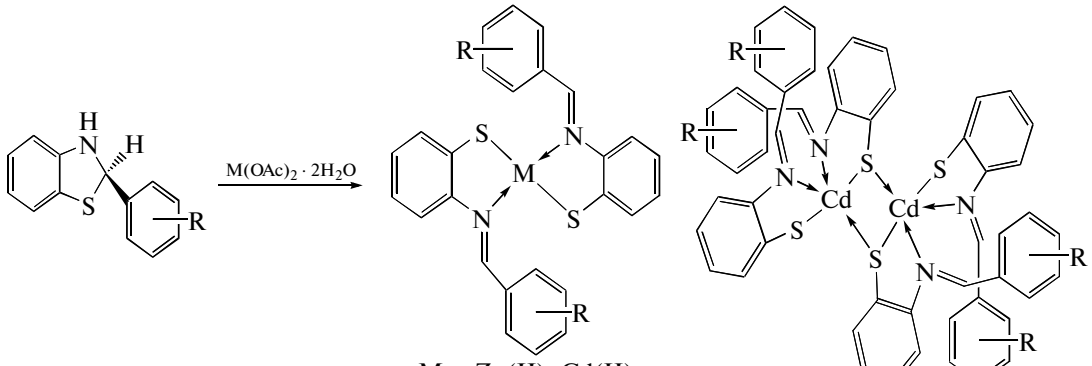
Cu(II), and Zn(II), L = substituted salicylaldehyde (5-H, 5-CH_3, 5-OCH_3, 5-NO_2, and 5-C1) and X = Cl have been synthesized and characterized. An octahedral structure for Ni(II) and Zn(II) and a distorted octahedral structure for Cu(II) chelates have been proposed. These structures look like the structures of series of *N*-(substituted phenyl)-*N'*-(naphtha[1,2-d]thiazol-2-yl)urea and thiourea derivatives. All the Schiff-bases and their metal chelates have been screened for their biological activity against *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. In comparison, the metal chelates possess more antibacterial [113] activity than the uncomplexed Schiff-bases.

A stable cobalt complex of phthalylsulphathiazole, $Co^{II}(PST)(H_2O)_4] \cdot 2H_2O$, has been synthesized and characterized by vibrational FTIR and Raman spectroscopic data reveal that the ligand would be doubly deprotonated. Spectroscopic and chemical data let us suggest that the $N_{thiazolic}$ and $N_{sulfonamide}$ atoms could be the binding sites for the Co^{2+} ion to the phthalylsulfathiazole moiety showed antibacterial activity similar to the ligand activity against *Candida albicans*. Complex did not show direct mutagenicity with the Ames test in the range of assay doses nor hemolytic effects to human erythrocytes in vitro at concentrations in which it is active. The phytotoxicity of Co(II) complex, evaluated with the Allium test, was similar to the phthalylsulfathiazole one in the whole tested range [114]. The mixed ligands Ni(II) complexes afforded by the reaction of $[Ni(L)_4Cl_2]$ with dianion of 1,1-dicyano-2,2-ethylenedithiolate ligand (i-MNT). The crystal and molecular structures of the studied Ni(II) compounds reveal the same distorted square-planar geometry for complexes. Representative reaction of the synthesis of $[Ni(i\text{-}MNT)(2a\text{-}5mt)_2]$ is:



The (i-MNT) ligand is coordinated with the two sulfur atoms and the endocyclic nitrogen atom of the two 2-amino-5-methyl thiazole or 2-amino-2-thiazoline or imidazole ligands. The isolated neutral, diamagnetic and of square-planar geometry complexes are of interest, since they meet the necessary properties for various biological tests. In the cyclic voltamograms of the complexes recorded in DMSO solution and in 1/2 DMSO/buffer solution, the expected waves attributed to redox couples and the corresponding potentials, characteristic for Ni(II) complexes have been recorded. The study of the interaction of the complexes with CT DNA has been performed with UV spectroscopy and cyclic voltammetry and has revealed that the complexes can bind to DNA. UV spectroscopic titrations have been used in order to calculate the binding strength of the complexes with CT DNA which is mirrored in the intrinsic binding constant (K_b). Cyclic voltammetric studies have shown that complexes can bind to CT DNA by both intercalation and electrostatic interaction. Competitive binding studies with EB with fluorescence spectroscopy have shown that the interaction between DNA–EB complex and the complexes can release EB from its DNA complex, indicating that they can bind to DNA probably via the intercalative mode [115].

A series of mononuclear unit distorted tetrahedral Schiff base zinc(II) complexes with various substituents on the pendent phenyl ring, $[Zn(R\text{–}Ph\text{–}C(H)=N\text{–}C_6H_4\text{–}S)_2]$, R = 2,4,6-trimethyl, 2,6-dichloro, 4-Cl, H, 4-Et, 4-OMe, 4-NMe_2, 4-NEt_2, have been synthesized and characterized. Synthesis of complexes is givenin the following Scheme:



It has been found that electronic property of the substituents, as well as their positions on the pendent phenyl rings of the Schiff base ligands affects the electronic absorption spectra of complexes. All the complexes are luminescent in CH_2Cl_2–toluene glass at 77 K, and the emission wavelengths were correlated with the Hammett constant of the substituents on the pendent phenyl rings. The analogy cadmium complexes, [Cd(R–Ph–C(H)=N–C_6H_4–$S)_2$], R = 2,4,6-trimethyl and [Cd_2(R–Ph–C(H)=N–C_6H_4–$S)_4$], R = 4-Et, 4-OMe, NMe_2, were synthesized but they have a dinuclear structure in solid state. Cadmium complex also give emission spectra in CH_2Cl_2–toluene glass at 77 K. These zinc and cadmium complexes with N_2S_2-Schiff base ligand are a new class of luminescent compounds [6] and careful derivatization of the substituents on the pendent phenyl rings permits a fine tuning of emission wavelength [116].

SPECTRAL CHARACTERISTICS

Magnetic moment and electronic spectra. When the crystal structure is formed, magnetic moment of a given ion participating in this structure depends on oxidation state, the symmetry and the strength of the crystal field and the nature of the chemical bond. The nature of ligand field around the metal ion and geometry of metal complexes have been deduced from the electronic spectra [5] and magnetic moment data of the complexes. Electronic spectral data of the thiazole derived ligands and their metal complexes which contained absorption reasons, band assignments and proposed geometry of the complexes. Ligands show strong peaks at 448, 380, and 259 nm. The two strong bands are attributed to the benzene π–π^* and imino π–π^* transitions. These bands are not significantly affected by the chelation and also know intraligand charge transfer (ILCT), the third band in the spectra of the ligand is assigned to the n–π^* transition. In the metal complexes this band shifted to a longer wavelength with increasing intensity. This shift may be attributed to the donation of lone pairs of electron of nitrogen atoms of the ligands to the metal ions.

IR spectroscopy. Practically all the ligands and metal complexes have been characterized in detail by recording their IR spectra. The infrared spectra of ligands show a band around 3450–3250 cm^{-1} due to hydrogen bonding. The ligands show bands in the regions 3250–3050 cm^{-1} assigned to the ν(N–H) of hydrazine or ν(N–H) imidazole moiety. The free ligands shows absorption bands in the range ~1650 cm^{-1} characteristics of azomethine (C=N) [5, 6] group. The band due to the thiazole ring (C=N) was absorbed in the range 1600–1610 cm^{-1}, and the vibrational characteristics of thiazole ring have been found at ~2600 cm^{-1}. The bands assigned to the ν(C=N) is shifts to the lower frequency which indicates the involvement of nitrogen of Schiff base in chelation. This shift indicates the coordination of ligand to metal atom by the nitrogen of the azomethines. The practically unchanged (C–S–C) at 685 cm^{-1} [33] of the thiazole ring confirmed that the thiazole group itself does not coordinate to metal center by sulfur atoms. The C–S–C group's vibrations of thiazole ring in free ligands occur in the range ~705 cm^{-1}. IR spectra reported [103] the formation of the Schiff base, o-vanillidene–2-aminobenzothiazoleis noted from the absence of C=O and NH_2 peaks in the spectrum of the ligand. Co(II), Mn(II), and Ni(II) complexes show abroad band at ~3400 cm^{-1} and a new band spectra reported by at ~860 cm^{-1}. These bands may probably be due to the vibrations of coordinated water molecules. However, these bands are not observed in the Cu(II) and Zn(II) complexes indicate the absence of coordinated water molecules. The band at 1662 cm^{-1} due to the azomethine group of the Schiff base underwent a shift to lower frequency (1632–1618 cm^{-1}) after complexation, indicating the bonding In the low frequency region, the band of medium intensity observed for the complexes in the region 430–470 cm^{-1} is attributed to (M–O) and in the region 560–580 cm^{-1} to (M–N). The (C=N) at 1563 cm^{-1} and (C–S–C) at 748 cm^{-1} of the thiazole ring remains unchanged demonstrated that the thiazole group does not coordinate to metal by neither nitrogen nor sulphur atom. All the IR data of the Schiff bases and its metal complexes imply that the Schiff base behaves as bidentate and is bonded to the metal ion through phenolic oxygen and imino nitrogen of azomethine group.

NMR spectroscopy. In addition to UV-Vis and IR studies, some diamagnetic complexes and their ligands have been characterized by NMR spectroscopy. The Schiff bases exhibited signals due to all the expected protons in their expected region and have been found from the integration curve equivalent to the total number of protons deduced from the proposed structures these were compared with the reported signals of known comparable compounds and give further support for the compositions of the new ligands as well as their complexes. Comparison of chemical shift of uncomplexed Schiff bases with those of corresponding zinc complexes show that some of the resonance signals underwent a shift upon complexation. In each case proton assigned to aromatic and azomethine moieties were found at ~7.1–8.1 and 6.8 ppm in the spectra of Schiff bases. The protons due to azomethine and aromatic groups underwent a downfield shift of 0.9–1.0 ppm in the complexes indicating coordination of these groups with the metal ion. ^{13}C NMR spectra likewise showed similar diagnostic features for the Schiff as well as their metal complexes.

ESR spectroscopy. The ESR spectra of the metal chelates provide information about hyperfine and super hyperfine structures which are important in studying the metal ion environment in the complexes, i.e. the geometry, nature of the ligating sites from the Schiff bases. The EPR spectrum of copper complex

[103] is recorded at 300 and 77 K. The 300 K spectrum shows an isotropic pattern for copper ions in solid state is due to the tumbling motion of the molecules. The magnitude of the ligand hyperfine splitting is similar in both the parallel and perpendicular spectrum but the copper hyperfine splitting is much larger in the parallel spectrum. The ESR spectra of copper complex possess characteristics spectrum having symmetric bands with two g values ($g_\parallel$ and $g_\perp$). The $g_\parallel$ value less than 2.3 and α^2 value of 0.764 suggest the covalent character of the metal ligand bond. The trend $g_\parallel > g_\perp > g_e$ (free ion value = 2.0023) for the complex shows that the unpaired present is in the $d_{x^2-y^2}$ of the Cu^{2+} ion. The $g_\parallel/A_\parallel$ value of the complex is 119 cm suggesting the square planar geometry of Cu(II) complex. The ESR spectra of the complexes in polycrystalline state exhibit broad signals which are attributable to dipolar broadening and enhanced spin-lattice. The anisotropic spectra are recorded for these complexes at liquid nitrogen temperature. The spectra are anisotropic at high field and the three peaks of low intensity in the weaker field region are taken as originating from $g_\parallel$ and $g_\perp$ are computed from the spectra using DPPH free radicals as g markers. This observation suggests a distorted octahedral geometry around Cu(II) center. The distortion may originate largely due to the thioether binding to the copper center. This is supported by the strong preference of thioether to the copper ion when it is part of the ligand to form a five-membered chelate ring in which the other donors are N or O. The isotropic term is basically due to a Fermi contact interaction and is related mainly to the degree of covalency of the complex, whereas the anisotropic interaction arises from a dipolar interaction between the ligand and the metal ion [6]. Since the ligand hyperfine interaction is mainly due to the isotropic term, this is confirmatory evidence that the azomethine group is bonded to the copper ion in this complex. The polarization produced by the uneven distribution of d-electron density on the inner core s-electron is calculated from the dipolar term (P) and the Fermi contact (κ) by the expression:

$$P = 2\gamma Cu\beta_o\beta_N(r-3) = 0.036\ cm^{-1},$$

$$\kappa = (A^0/P) + g^0.$$

THERMOGRAVIMETRIC ANALYSIS

Very few references are available on the thermal properties thiazole derived metal complexes. Polymorphism is very common with different melting point, solubility, chemical reactivity and stability. It has been reported [103] that the Co(II), Mn(II) and Ni(II) complexes show a loss in weight between 70 and 190°C indicating that the coordinated water molecules are present in the complexes. The Cu(II) and Zn(II) complexes do not show any loss in weight up to 200°C, reveals that crystal water molecules and coordinated water molecules are not present in the complexes. The TG curve in the 345–510°C range suggest that the loss in the weight for all complexes corresponds to evaporation of ligand in the range 510–740°C, the loss in the weight corresponds to the remaining organic ligand molecule.

X-RAY DIFFRACTION

To obtain further evidence about the structure of metal complexes X-ray diffraction was performed. The diffractrograms obtained for Schiff base metal complexes indicates crystalline nature for the complexes. It has been reported [103] that the pattern of the Schiff base are differs from its metal complexes, which may be attributed to the formation of well-defined distorted crystalline structure. Probably this behavior is due to the incorporation of water molecules into the coordination sphere.

ANTIBACTERIAL STUDY OF THIAZOLE MOIETY CONTAINED LIGAND AND THEIR COMPLEXES

The increased activity of metal complexes can be explained on the basis of chelation theory. Chelation reduces [5, 6] the polarity of the metal ion considerably, mainly because of the partial sharing of its positive charge with donor groups and possible p-electron delocalization on the whole chelate ring. Chelation can reduce not only the polarity of the metal ion, but it increases the lipophilic character of the chelate, and the interaction between metal ion and the lipid is favored. This may lead to the breakdown of the permeability barrier of the cell, resulting in interference with the normal cellular processes. If the geometry and charge distribution around the molecule are incompatible with the geometry and charge distribution around the pores of the bacterial cell wall, penetration through the wall by the toxic agent cannot take place and this will prevent the toxic reaction within the pores. Effect of substitution on the phenyl ring on the antibacterial activity has been also examined. Substitution on the phenyl ring attached to the thiazole group showed interesting structure activity relationships. When the 4-position of phenyl ring was substituted with the –OH group, the resulting ligand as well as the complex showed a moderate increase in the antibacterial activity when compared to unsubstituted phenyl derivative. The same trend has been observed for OCH_3 and CH_3 derivatives. This suggests that the electron-donating groups on the thiazole moiety, is favorable. Further, substitution of the 4-position of phenyl ring with electron withdrawing groups such as NO_2, Cl, and Br indicated that these ligands and complexes possess less activity than the other complexes. In summary, hydroxyl, methoxy and methyl substituents on the phenyl group of the thiazole moiety imparts good antibacterial activity, whereas electron-withdrawing groups on the phenyl ring lead to a de-

crease in antibacterial activity. However, in all cases the activity has been greater for the metal complexes than the free ligands. The antibacterial activity [5, 6] of these ligands and their complexes can be also ascribed to hydrogen bond formation between the nitrogen (>C=N) atom of the compound and some bio receptors in the cell of bacteria which in turn block the synthesis of proteins by inhibiting the movement of ribosome along RNA.

APPLICATION OF COMPLEXES OF THIAZOLE

2-(4-Aminophenyl) benzothiazoles display potent and selective antitumor activity against inter alia breast, ovarian, colon, and renal cell lines, but their mechanism of action, though yet to be defined. Metabolism is suspected to play a central role in the mode of action of these benzothiazoles since drug uptake and biotransformation were observed in sensitive cell lines (e.g., breast MCF-7 and MDA 468 cells) in vitro, whereas insensitive cell lines (e.g., prostate PC 3 cells) showed negligible uptake and biotransformation. *N*-Acyl derivatives of the arylamines have been synthesized, and in vitro studies confirm *N*-acetylation and oxidation as the main metabolic transformations of 2-(4-aminophenyl) benzothiazoles, with the predominant process being dictated by the nature of the substituent.

CONCLUSIONS

Great efforts have been made to the incorporation of biomolecules into the synthesis of biologically potent ligands and their metal complexes and to enable specific target. Aromatic Schiff bases or their metal chelates are being used to catalyze reactions on oxygenation, hydrolysis, electro reduction and decomposition. Complexes of thallium(I) with the benzothiazolines show antibacterial activity against pathogenic bacteria. Schiff base ligand containing cyclobutane and thiazole rings, show antimicrobial activity. Schiff bases derived from sulfane thiadiazole and salicylaldehyde or thiophene-2-aldehydes and their complexes show toxicities against insects. Schiff bases (thiadiazole derivatives with salicylaldehyde or *o*-vanillin) and their metal complexes with Mo(IV) shows insecticidal activities against bollworm and promote cell survival rate of mung bean sprouts. Schiff bases of thiadiazole have good plant regulator activity towards auxin and cytokine.

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