Synthesis, characterization and antimicrobial studies of N, O, S containing ligands and their transition metal complexes

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Award of the Degree of

Master of Philosophy
in
Chemistry

by
Biju Jacob
(Reg. No. 1540026)

Under the Guidance of
Riya Datta
Associate Professor

CHRIST
UNIVERSITY
BENGALURU, INDIA

Declared as Deemed to be University under Section 3 of UGC Act 1956

Department of Chemistry

CHRIST UNIVERSITY
BENGALURU, INDIA
December 2016

CERTIFICATE

This is to certify that the dissertation submitted by Biju Jacob (Reg. No.140026) titled '**Synthesis, characterization and antimicrobial studies of N, O, S containing ligands and their transition metal complexes**' is a record of research work done by him during the academic year 2015-2016 under my supervision in partial fulfillment for the award of Master of Philosophy in Chemistry.

This dissertation has not been submitted for the award of any degree, diploma, associateship, fellowship or other title. It has not been sent for any publication or presentation purpose. I hereby confirm the originality of the work and that there is no plagiarism in any part of the dissertation.

Place:Bengaluru
Date:

Dr Riya Datta
Associate Professor
Department of Chemistry
Christ University, Bengaluru

Dr Louis George
Associate Dean of Science and Head
Department of Chemistry
Christ University, Bengaluru

DECLARATION

I Biju Jacob hereby declare that the dissertation, titled '**Synthesis, characterization and antimicrobial studies of N, O, S containing ligands and their transition metal complexes**' is a record of original research work undertaken by me for the award of the degree of Master of Philosophy in Chemistry. I have completed this study under the supervision of Dr Riya Datta, Associate Professor, Department of Chemistry.

I also declare that this dissertation has not been submitted for the award of any degree, diploma, associateship, fellowship or other title. It has not been sent for any publication or presentation purpose. I hereby confirm the originality of the work and that there is no plagiarism in any part of the dissertation.

Place: Bengaluru
Date:

Biju Jacob
Reg No.1540026
Department of Chemistry
Christ University, Bengaluru

Acknowledgement

I am extremely thankful to all those who have provided me help and motivated me during the course of my research work. I would like to thank the management of Christ University for giving me the opportunity to continue my studies. I express sincere thanks to my supervisor Dr Riya Datta for providing guidance and support in carrying out research.

I am grateful to Vice Chancellor Rev Dr Fr Thomas C Mathew, and Prof. Chandrasekharan K A, Personnel officer, for providing me all the help and necessary facilities. I express my gratitude to Dr Louis George, Associate Dean of Science and Head, Department of Chemistry for his valuable advice and encouragement.

I thank Dr Anitha Varghese, MPhil co-ordinator for her valuable suggestions and support. I express my gratitude to Dr Surendra Kulkarni, Dean of Science. I am extremely thankful to Dr Nanje Gowda N M, former Dean of Science, for providing me apt advice in due time to fulfil my research. I recall with gratitude all the faculty members of the Department of Chemistry. I express my sincere thanks to the Finance Officer, Christ University for the financial assistance for my research.

I sincerely thank Mrs Akshaya Upadyaya and Mrs Arunima Chakraborty for their help and valuable suggestions throughout my research. I am grateful to my friends for their assistance during my research. I extend my gratitude to all the teaching and non-teaching staff of Christ University.

I convey my special acknowledgement to the Heads of Institutions of CUSAT (SAIF, Kochi), St Joseph's College Devagiri, Kozhikode and also to Anthem Bio-Science Private Limited.

Most importantly, I thank my Community where I belong for their constant support, guidance and encouragement. I am indeed grateful to Almighty God, my life, light and way for having made everything possible through strength, courage and inspiration to do the research work.

Date:

Place: Bengaluru Biju Jacob

Contents

List of Tables

List of figures

Chapter 1

Introduction

The coordination chemistry of transition metals and their derivatives has got much attention in recent years [1] because many of the biological processes which are fundamental to life are controlled by transition metals [2]. Many of these coordination compounds possess remarkable biological properties such as antibacterial, analgesic [2-3], antifungal, antimalarial [4-6], antiviral [7-11], anticancer [12-17], antidiabetic [18-23], anti-HIV [24-27] activities and plant growth regulating activity [14] [24] [28-29]. The O- or N- terminals of proteins can be coordinated to metals in numerous ways and thus can play a vital role in the function of biological macromolecules [2]. Nitrogen, oxygen and sulphur donor ligands possess a range of biological applications like antitumor, antibacterial, antifungal, antimalarial and antiviral activities [7] [10] [85] and they can bind the biomolecules at their active sites [30-31]. Macrocycles which contain nitrogen have a strong tendency to form stable transition metal complexes [26] [32]. Coordination of bi, tri and tetradentate ligands containing nitrogen, oxygen or sulphur donor atoms with various transition and inner-transition metal play an important role in biological systems [33].

Due to the excellent donor properties of azo group, the complexes containing azo groups exhibits excellent antimicrobial activity [34]. The biological activity of azo compounds is due to the presence of azomethine linage (C=N) which is a basic structural necessity for biological activity [14] [23] [35]. Remarkable enhanced antibacterial [23] [36], antifungal [23] [36] and anticancer activities [14] [23] [37-39] have been observed for complexes containing azomethine linkage.

Hydrazones which belongs to Schiff base family has the functional group (>N-N=C<) in which the azomethine group is adjacent to another nitrogen atom [40-41]. The biological activities of hydrazones are due to the presence of lone pair electrons of sp^2 hybridized orbitals of azomethine nitrogen [41-43]. Hydrazones which contain an azomethine proton (–NHN=CH–) is therapeutically important for new drug development [41-43]. The additional donor site, >C=O of aroyl, acyl and heteroaroyl hydrazone Schiff base compounds makes the hydrazones more flexible and versatile. This additional donor site makes hydrazones as good polydentate chelating ligand and can coordinate with various transition and inner transition metals in numerous ways [40]. Hydrazones and their metal complexes show varied applications in the fields such as antifungal, antibacterial, antioxidative and cytotoxic studies [44]. They have been found to be potential chemotherapeutic agents [45].

Furoic acid hydrazones and their transition metal complexes are of great interest due to their microbial inhibition [40] [46]. Benzofuran based metal complexes also exhibit biological activities as anti-infective agents, like antifungal, antiprotozoal, and antitubercular, and also in the treatment of antiarrhythmic and cardiovascular diseases [47].

Schiff base ligands having oxygen, nitrogen and sulphur donor sites and their coordination complexes [34] [48] have been reported as excellent therapeutic agents. They exhibit inhibitory activities against bacteria, fungi [34], and certain type of cancers [34] and they have biochemical, clinical and pharmacological properties [49].

Amino quinazoline derivatives were found to have phosphodiasterase property and they work as potent anticancer agents [14] [60]. Triazole compounds possess a wide range of biological activities such as antifungal (fluconazole), antidepressant (trazodone), and anticancerous (vorozole, anastrozole and letrozole) [14] [61]. Copper(II) complexes of triazoles have been studied extensively and proved to have therapeutic properties against tuberculosis, gastric ulcers, rheumatoid arthritis and cancers [62].

1.1 Schiff base ligands

Schiff base which is formed by the condensation reaction of primary amines with carbonyl compounds [109-110] have been used as ligands for coordinating various transition and inner transition metal ions. They can be used also for coordinating anions [111]. Schiff bases have very interesting chemical properties because they may contain variety of substituent with active donor sites, electron withdrawing or electron donating active sites. Most of the Schiff bases are highly stable because of the strength of azomethine (C=N) bond. Its stability also depends on the basicity of amino group, steric factors and chelating effect. Presence of functional groups like –OH or –SH may increase the chelation leading to the formation of five or six membered ring. Scheme of Schiff base formation is given in following **Fig. 1.1**.

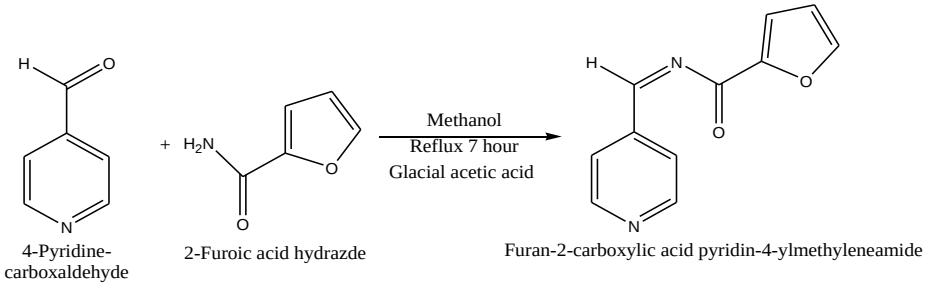


Fig. 1.1 Scheme of Schiff base formation

1.2. Schiff base metal complexes

Schiff bases are one of the most flexible and versatile group of ligands due the presence of various active donor sites they possess. This versatility has made them polydentate ligand and thus can form numerous complexes with various transition and inner transition metal ions [40]. Schiff bases and its metal complexes have a wide variety of interesting properties and applications which include catalytic, synthetic, analytical, biochemical, electrochemical sensing and therapeutic applications. Schiff bases have high affinity for chelation with transition metal ions. The stability of metal complexes depends on chelating effect. The presence of chelating agents like carbonyl, hydroxyl or thio groups close to the proximity of azomethine (C=N) linkage increases the chelation and thus stability of metal complexes. Schiff base and its metal complexes are thus of recent research interest comprising of various research fields such as organometallic, inorganic, bioinorganic, catalytic and electrochemical [112-113]. In our present work we focus on oxygen, nitrogen and sulphur containing ligands and their transition metal complexes of nickel and copper metal ions. Some examples of Schiff base metal complexes containing nitrogen, oxygen and sulphur donor atoms are given the following **Fig. 1.2**.

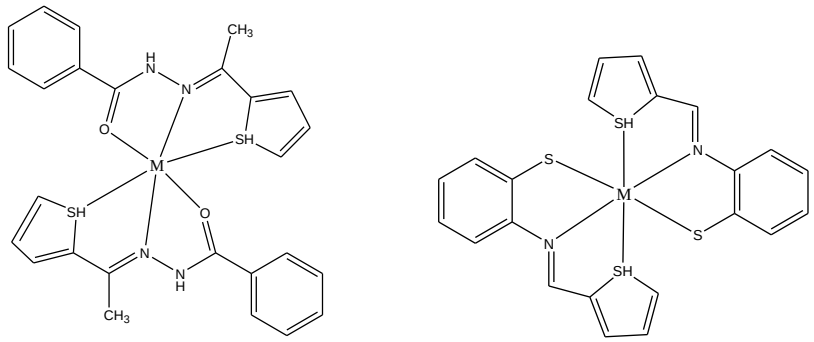


Fig. 1.2 Schiff base metal complexes

1.3 Synthesis of Schiff bases and their metal complexes

The Schiff base metal complexes are synthesized by two ways, template synthesis and the other one is conventional method.

1.3.1 Conventional method

In conventional method the ligand is synthesized prior and then the metal salt is added to the synthesized ligand to form the complex.

Synthesis of the ligand and metal complex

A general scheme for synthesis of the ligand and metal complex is given in **Fig. 1.3** and **Fig. 1.4**.

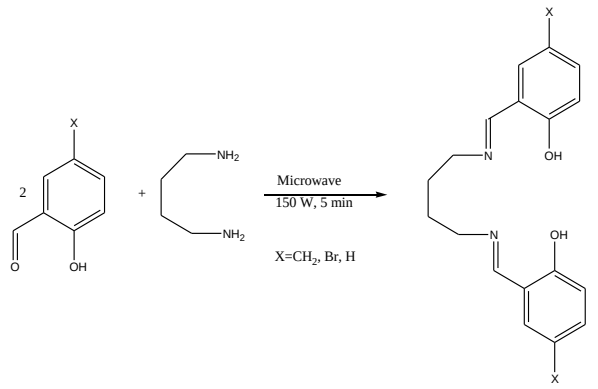


Fig. 1.3 Scheme of synthesis of ligand

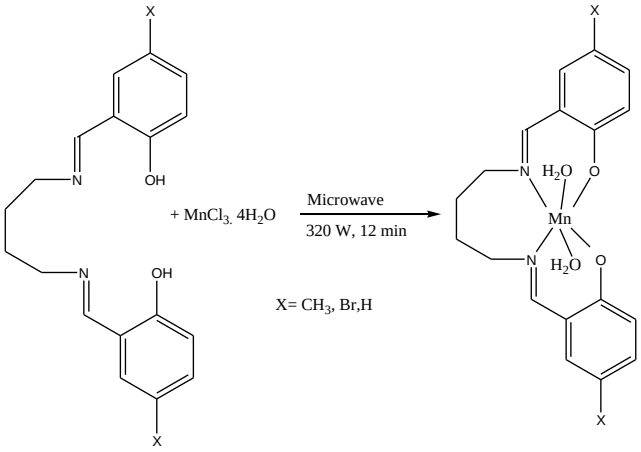


Fig. 1.4 Scheme for the synthesis of Schiff base metal complexes

1.3.2 Template synthesis

Template synthesis is a single step synthesis of metal complexes, i.e., without the isolation and purification of the ligand, the complex is synthesized. It is an in situ reaction [41] [43]. The condenstion of carbonyl compund and amine, and the coordination of metal takesplace in a single step reaction [114]. Template can be defined as "any species that organizes an assembly of molecular building blocks by non-covalent interraction favouring of a specific product" [121]. Template synthesis is a useful technique to achieve the synthsis of assemblies that have unusal topologies such as macrocycles, rotaxanes, helicates and catananes [115].

Template synthsis can be carried out in several ways, thermodynamic, microwave irradiation and ultrasonication method. In thermodynamic processes, one of the reactants binds the template and an equilibirium is formed. This equilibirium is shifted towards the formation of a specific product. Microwave irradiation is an irreversible process leading to the formation of wanted product. In this case the reaction can be very fast and shorter time with high yield. A general scheme for the template synthsis is given in **Fig. 1.5**.

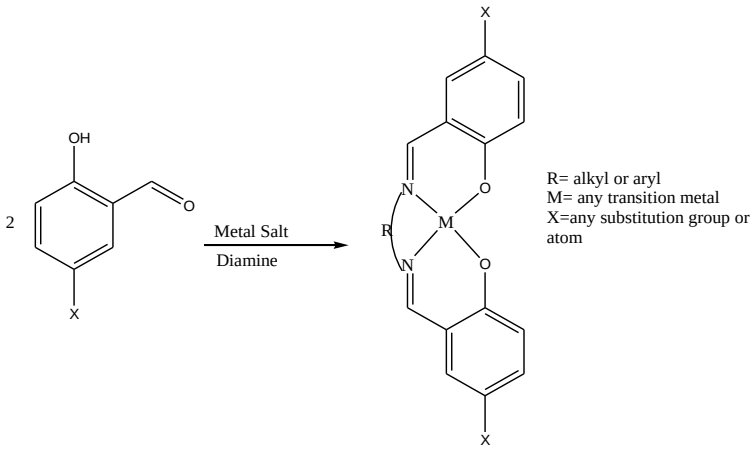


Fig. 1.5 Scheme of Template synthesis of Schiff base metal complexes

1.4 The role of metal ions in biological systems

Life has evolved from inorganic materials and thus inorganic chemistry is vital to all biological processes. Though many biological reactions are already known most of the things are yet to be exposed. Inorganic chemistry is an interdisciplinary science and it covers different areas like biochemistry, biology, physiology, medicine, agriculture, physics, and environmental sciences. All the biological activities are mediated by specific proteins or enzymes, most of which require one or more metal ions for their activity and their structural integrity. Enzymes bound metal ions, by virtue of their unique coordination chemistry, may

provide binding sites of the substrates confer and stabilize the appropriate conformation of the enzymes and may function as catalytic centers. Lability and inertness of metal ligand bonds, stereochemistry, stability, magnetic and redox properties of metal ligand complexes manifest themselves in all the reactions of metal ions in metalloproteins and metalloenzymes.

1.5 Biological importance of nickel, copper and its complexes

Nickel and copper are considered as essential elements in animals, microorganisms and plants and it is a constituent of many of the enzymes and proteins [116]. Nickel is found in a number of groups of bacteria. It is an essential element in the biosynthesis of the hydrogenase and carbon monoxide dehydrogenase. Several plant species also contain nickel containing protein. Urease from jack beans is rich in nickel protein. It is a constituent part of all organs of vertebrates. Nickel deficiency may cause reduced growth, histological change, reduced resorption, anaemia and thus vital to metabolism and life [117-118].

Many of the proteins contain copper ions. They are involved in many biological processes such as electron transfer and oxidation- reduction of various organic moieties. In fact copper containing proteins acts as redox catalysts. Dicopper proteins are involved in hydroxylation, one electron oxidation of pseudo azurine/one electron reduction of NO_2^-.

Schiff bases have excellent therapeutic properties. Its medicinal property can be enhanced by coordination with metal ions. Copper and nickel complexes have several biological applications including antibacterial, antifungal, antiviral, analgesic antitumour etc. So these metals can be utilized for combating diseases of human body.

1.6 Antimicrobial properties of ligands and their metal complexes

The characteristic properties of coordination compounds depends on the nature of donor atom, steric factors, nature of the metal ion, structure of the coordinating ligand, the metal-ligand interaction and the nature of the solvent employed [50-51]. Schiff bases show excellent biological activities against many pathogenic bacteria, fungi and against certain cancerous cells [34] [48-49]. Schiff bases having chelative donor sites like nitrogen, oxygen and sulphur when coordinated to metal ions an enhanced biological activity is observed [9] [50] [52]. Factors controlling antimicrobial activities are the following,

1. Chelation
2. Cell permeability and
3. Lipophilicity

Generally metal chelates have enhanced activity than the free ligand [14] [56-57]. As chelation increases biological activity also increases [9] [50] [52] because chelation increases the cell permeability. On chelation the polarity of the metal ion reduces and the lipophilic nature of the metal ion enhances [7] [37] [53]. This enhanced lipophilic nature favours cell permeability. Thus metal atoms can permeate more effectively through the lipid layer of microbes destroying them or blocking their active sites [28] [30] [51-52]. Thus one of the ways to improve the biological activity is to increase the number of chelate rings [9] [37] [53-54].

1.7 Objectives of the study

- To synthesize ligands containng sulphur, nitrogen and oxygen
- To synthesize metal complexes of copper and nickel using the synthesized ligands
- To characterize the synthesized ligands and metal complexes
- To conduct antimicrobial studies of the synthesized ligands and metal complexes

Conclusion

Even though advanced modern science and technology hails for its invention and innovation to control the infectious diseases, microbial resistance to antibiotics is a severe issue to be confronted and solved [9] [28] [48] [50] [63]. Thus inorganic chemistry opens a new way for new research and development.

Chapter 1

Introduction

The coordination chemistry of transition metals and their derivatives has got much attention in recent years [1] because many of the biological processes which are fundamental to life are controlled by transition metals [2]. Many of these coordination compounds possess remarkable biological properties such as antibacterial, analgesic [2-3], antifungal, antimalarial [4-6], antiviral [7-11], anticancer [12-17], antidiabetic [18-23], anti-HIV [24-27] activities and plant growth regulating activity [14] [24] [28-29]. The O- or N- terminals of proteins can be coordinated to metals in numerous ways and thus can play a vital role in the function of biological macromolecules [2]. Nitrogen, oxygen and sulphur donor ligands possess a range of biological applications like antitumor, antibacterial, antifungal, antimalarial and antiviral activities [7] [10] [85] and they can bind the biomolecules at their active sites [30-31]. Macrocycles which contain nitrogen have a strong tendency to form stable transition metal complexes [26] [32]. Coordination of bi, tri and tetradentate ligands containing nitrogen, oxygen or sulphur donor atoms with various transition and inner-transition metal play an important role in biological systems [33].

Due to the excellent donor properties of azo group, the complexes containing azo groups exhibits excellent antimicrobial activity [34]. The biological activity of azo compounds is due to the presence of azomethine linage (C=N) which is a basic structural necessity for biological activity [14] [23] [35]. Remarkable enhanced antibacterial [23] [36], antifungal

[23] [36] and anticancer activities [14] [23] [37-39] have been observed for complexes containing azomethine linkage.

Hydrazones which belongs to Schiff base family has the functional group (>N-N=C<) in which the azomethine group is adjacent to another nitrogen atom [40-41]. The biological activities of hydrazones are due to the presence of lone pair electrons of sp^2 hybridized orbitals of azomethine nitrogen [41-43]. Hydrazones which contain an azomethine proton (–NHN=CH–) is therapeutically important for new drug development [41-43]. The additional donor site, >C=O of aroyl, acyl and heteroaroyl hydrazone Schiff base compounds makes the hydrazones more flexible and versatile. This additional donor site makes hydrazones as good polydentate chelating ligand and can coordinate with various transition and inner transition metals in numerous ways [40]. Hydrazones and their metal complexes show varied applications in the fields such as antifungal, antibacterial, antioxidative and cytotoxic studies [44]. They have been found to be potential chemotherapeutic agents [45].

Furoic acid hydrazones and their transition metal complexes are of great interest due to their microbial inhibition [40] [46]. Benzofuran based metal complexes also exhibit biological activities as anti-infective agents, like antifungal, antiprotozoal, and antitubercular, and also in the treatment of antiarrhythmic and cardiovascular diseases [47].

Schiff base ligands having oxygen, nitrogen and sulphur donor sites and their coordination complexes [34] [48] have been reported as excellent therapeutic agents. They exhibit inhibitory activities against bacteria, fungi [34], and certain type of cancers [34] and they have biochemical, clinical and pharmacological properties [49].

Amino quinazoline derivatives were found to have phosphodiasterase property and they work as potent anticancer agents [14] [60]. Triazole compounds possess a wide range of biological activities such as antifungal (fluconazole), antidepressant (trazodone), and anticancerous (vorozole, anastrozole and letrozole) [14] [61]. Copper(II) complexes of triazoles have been studied extensively and proved to have therapeutic properties against tuberculosis, gastric ulcers, rheumatoid arthritis and cancers [62].

1.2 Schiff base ligands

Schiff base which is formed by the condensation reaction of primary amines with carbonyl compounds [109-110] have been used as ligands for coordinating various transition and inner

transition metal ions. They can be used also for coordinating anions [111]. Schiff bases have very interesting chemical properties because they may contain variety of substituent with active donor sites, electron withdrawing or electron donating active sites. Most of the Schiff bases are highly stable because of the strength of azomethine (C=N) bond. Its stability also depends on the basicity of amino group, steric factors and chelating effect. Presence of functional groups like –OH or –SH may increase the chelation leading to the formation of five or six membered ring. Scheme of Schiff base formation is given in following **Fig. 1.1**.

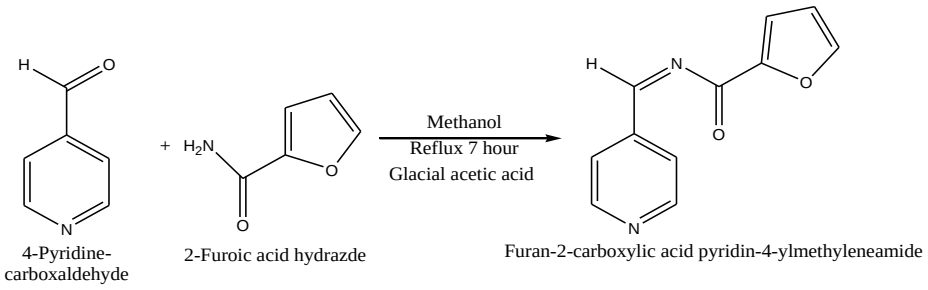


Fig. 1.1 Scheme of Schiff base formation

1.3. Schiff base metal complexes

Schiff bases are one of the most flexible and versatile group of ligands due the presence of various active donor sites they possess. This versatility has made them polydentate ligand and thus can form numerous complexes with various transition and inner transition metal ions [40]. Schiff bases and its metal complexes have a wide variety of interesting properties and applications which include catalytic, synthetic, analytical, biochemical, electrochemical sensing and therapeutic applications. Schiff bases have high affinity for chelation with transition metal ions. The stability of metal complexes depends on chelating effect. The presence of chelating agents like carbonyl, hydroxyl or thio groups close to the proximity of azomethine (C=N) linkage increases the chelation and thus stability of metal complexes. Schiff base and its metal complexes are thus of recent research interest comprising of various research fields such as organometallic, inorganic, bioinorganic, catalytic and electrochemical [112-113]. In our present work we focus on oxygen, nitrogen and sulphur containing ligands and their transition metal complexes of nickel and copper metal ions. Some examples of Schiff base metal complexes containing nitrogen, oxygen and sulphur donor atoms are given the following **Fig. 1.2**.

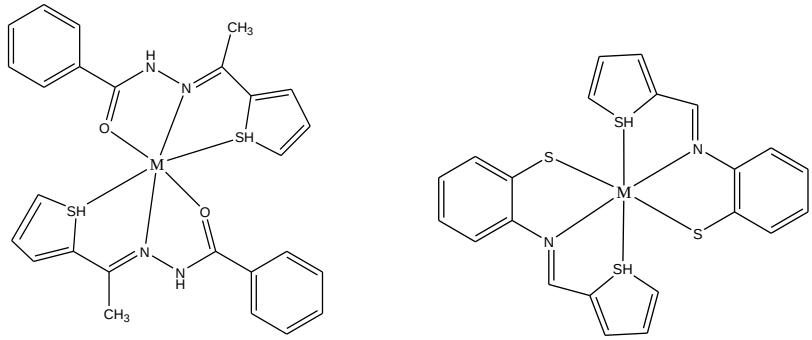


Fig. 1.2 Schiff base metal complexes

1.3 Synthesis of Schiff bases and their metal complexes

The Schiff base metal complexes are synthesized by two ways, template synthesis and the other one is conventional method.

1.3.1 Conventional method

In conventional method the ligand is synthesized prior and then the metal salt is added to the synthesized ligand to form the complex.

Synthesis of the ligand and metal complex

A general scheme for synthesis of the ligand and metal complex is given in **Fig. 1.3** and **Fig. 1.4**.

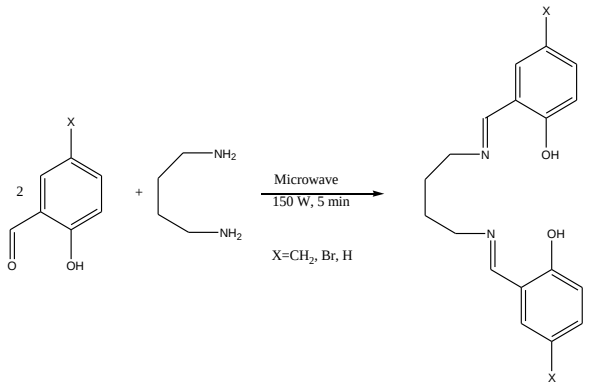


Fig. 1.3 Scheme of synthesis of ligand

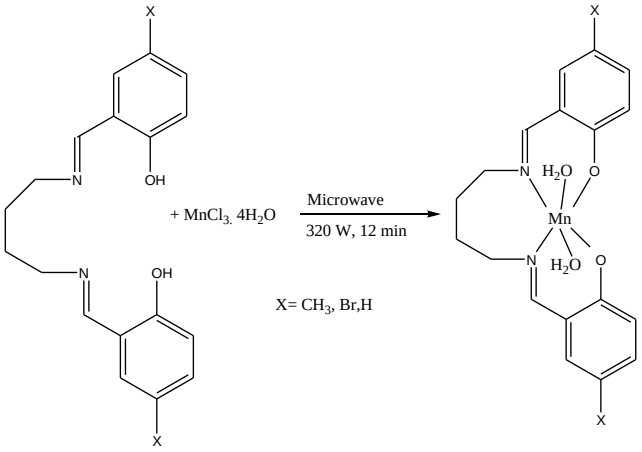


Fig. 1.4 Scheme for the synthesis of Schiff base metal complexes

1.3.2 Template synthesis

Template synthesis is a single step synthesis of metal complexes, i.e., without the isolation and purification of the ligand, the complex is synthesized. It is an in situ reaction [41] [43]. The condenstion of carbonyl compund and amine, and the coordination of metal takesplace in a single step reaction [114]. Template can be defined as "any species that organizes an assembly of molecular building blocks by non-covalent interraction favouring of a specific product" [121]. Template synthesis is a useful technique to achieve the synthsis of assemblies that have unusal topologies such as macrocycles, rotaxanes, helicates and catananes [115].

Template synthsis can be carried out in several ways, thermodynamic, microwave irradiation and ultrasonication method. In thermodynamic processes, one of the reactants binds the template and an equilibirium is formed. This equilibirium is shifted towards the formation of a specific product. Microwave irradiation is an irreversible process leading to the formation of wanted product. In this case the reaction can be very fast and shorter time with high yield. A general scheme for the template synthsis is given in **Fig. 1.5**.

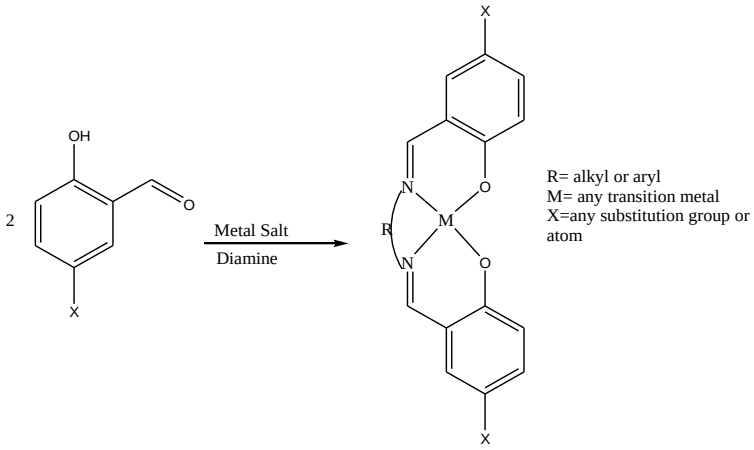


Fig. 1.5 Scheme of Template synthesis of Schiff base metal complexes

1.6 The role of metal ions in biological systems

Life has evolved from inorganic materials and thus inorganic chemistry is vital to all biological processes. Though many biological reactions are already known most of the things are yet to be exposed. Inorganic chemistry is an interdisciplinary science and it covers different areas like biochemistry, biology, physiology, medicine, agriculture, physics, and environmental sciences. All the biological activities are mediated by specific proteins or enzymes, most of which require one or more metal ions for their activity and their structural integrity. Enzymes bound metal ions, by virtue of their unique coordination chemistry, may provide binding sites of the substrates confer and stabilize the appropriate conformation of the enzymes and may function as catalytic centers. Lability and inertness of metal ligand bonds, stereochemistry, stability, magnetic and redox properties of metal ligand complexes manifest themselves in all the reactions of metal ions in metalloproteins and metalloenzymes.

1.7 Biological importance of nickel, copper and its complexes

Nickel and copper are considered as essential elements in animals, microorganisms and plants and it is a constituent of many of the enzymes and proteins [116]. Nickel is found in a number of groups of bacteria. It is an essential element in the biosynthesis of the hydrogenase and carbon monoxide dehydrogenase. Several plant species also contain nickel containing protein. Urease from jack beans is rich in nickel protein. It is a constituent part of all organs of vertebrates. Nickel deficiency may cause reduced growth, histological change, reduced resorption, anaemia and thus vital to metabolism and life [117-118].

Many of the proteins contain copper ions. They are involved in many biological processes such as electron transfer and oxidation- reduction of various organic moieties. In fact copper containing proteins acts as redox catalysts. Dicopper proteins are involved in hydroxylation, one electron oxidation of pseudo azurine/one electron reduction of NO_2^-.

Schiff bases have excellent therapeutic properties. Its medicinal property can be enhanced by coordination with metal ions. Copper and nickel complexes have several biological applications including antibacterial, antifungal, antiviral, analgesic antitumour etc. So these metals can be utilized for combating diseases of human body.

1.6 Antimicrobial properties of ligands and their metal complexes

The characteristic properties of coordination compounds depends on the nature of donor atom, steric factors, nature of the metal ion, structure of the coordinating ligand, the metal-ligand interaction and the nature of the solvent employed [50-51]. Schiff bases show excellent biological activities against many pathogenic bacteria, fungi and against certain cancerous cells [34] [48-49]. Schiff bases having chelative donor sites like nitrogen, oxygen and sulphur when coordinated to metal ions an enhanced biological activity is observed [9] [50] [52]. Factors controlling antimicrobial activities are the following,

4. Chelation
5. Cell permeability and
6. Lipophilicity

Generally metal chelates have enhanced activity than the free ligand [14] [56-57]. As chelation increases biological activity also increases [9] [50] [52] because chelation increases the cell permeability. On chelation the polarity of the metal ion reduces and the lipophilic nature of the metal ion enhances [7] [37] [53]. This enhanced lipophilic nature favours cell permeability. Thus metal atoms can permeate more effectively through the lipid layer of microbes destroying them or blocking their active sites [28] [30] [51-52]. Thus one of the ways to improve the biological activity is to increase the number of chelate rings [9] [37] [53-54].

1.7 Objectives of the study

- To synthesize ligands containng sulphur, nitrogen and oxygen

- To synthesize metal complexes of copper and nickel using the synthesized ligands
- To characterize the synthesized ligands and metal complexes
- To conduct antimicrobial studies of the synthesized ligands and metal complexes

Conclusion

Even though advanced modern science and technology hails for its invention and innovation to control the infectious diseases, microbial resistance to antibiotics is a severe issue to be confronted and solved [9] [28] [48] [50] [63]. Thus inorganic chemistry opens a new way for new research and development.

Chapter 1

Introduction

The coordination chemistry of transition metals and their derivatives has got much attention in recent years [1] because many of the biological processes which are fundamental to life are

controlled by transition metals [2]. Many of these coordination compounds possess remarkable biological properties such as antibacterial, analgesic [2-3], antifungal, antimalarial [4-6], antiviral [7-11], anticancer [12-17], antidiabetic [18-23], anti-HIV [24-27] activities and plant growth regulating activity [14] [24] [28-29]. The O- or N- terminals of proteins can be coordinated to metals in numerous ways and thus can play a vital role in the function of biological macromolecules [2]. Nitrogen, oxygen and sulphur donor ligands possess a range of biological applications like antitumor, antibacterial, antifungal, antimalarial and antiviral activities [7] [10] [85] and they can bind the biomolecules at their active sites [30-31]. Macrocycles which contain nitrogen have a strong tendency to form stable transition metal complexes [26] [32]. Coordination of bi, tri and tetradentate ligands containing nitrogen, oxygen or sulphur donor atoms with various transition and inner-transition metal play an important role in biological systems [33].

Due to the excellent donor properties of azo group, the complexes containing azo groups exhibits excellent antimicrobial activity [34]. The biological activity of azo compounds is due to the presence of azomethine linage (C=N) which is a basic structural necessity for biological activity [14] [23] [35]. Remarkable enhanced antibacterial [23] [36], antifungal [23] [36] and anticancer activities [14] [23] [37-39] have been observed for complexes containing azomethine linkage.

Hydrazones which belongs to Schiff base family has the functional group (>N-N=C<) in which the azomethine group is adjacent to another nitrogen atom [40-41]. The biological activities of hydrazones are due to the presence of lone pair electrons of sp^2 hybridized orbitals of azomethine nitrogen [41-43]. Hydrazones which contain an azomethine proton (–NHN=CH–) is therapeutically important for new drug development [41-43]. The additional donor site, >C=O of aroyl, acyl and heteroaroyl hydrazone Schiff base compounds makes the hydrazones more flexible and versatile. This additional donor site makes hydrazones as good polydentate chelating ligand and can coordinate with various transition and inner transition metals in numerous ways [40]. Hydrazones and their metal complexes show varied applications in the fields such as antifungal, antibacterial, antioxidative and cytotoxic studies [44]. They have been found to be potential chemotherapeutic agents [45].

Furoic acid hydrazones and their transition metal complexes are of great interest due to their microbial inhibition [40] [46]. Benzofuran based metal complexes also exhibit

biological activities as anti-infective agents, like antifungal, antiprotozoal, and antitubercular, and also in the treatment of antiarrhythmic and cardiovascular diseases [47].

Schiff base ligands having oxygen, nitrogen and sulphur donor sites and their coordination complexes [34] [48] have been reported as excellent therapeutic agents. They exhibit inhibitory activities against bacteria, fungi [34], and certain type of cancers [34] and they have biochemical, clinical and pharmacological properties [49].

Amino quinazoline derivatives were found to have phosphodiasterase property and they work as potent anticancer agents [14] [60]. Triazole compounds possess a wide range of biological activities such as antifungal (fluconazole), antidepressant (trazodone), and anticancerous (vorozole, anastrozole and letrozole) [14] [61]. Copper(II) complexes of triazoles have been studied extensively and proved to have therapeutic properties against tuberculosis, gastric ulcers, rheumatoid arthritis and cancers [62].

1.3 Schiff base ligands

Schiff base which is formed by the condensation reaction of primary amines with carbonyl compounds [109-110] have been used as ligands for coordinating various transition and inner transition metal ions. They can be used also for coordinating anions [111]. Schiff bases have very interesting chemical properties because they may contain variety of substituent with active donor sites, electron withdrawing or electron donating active sites. Most of the Schiff bases are highly stable because of the strength of azomethine (C=N) bond. Its stability also depends on the basicity of amino group, steric factors and chelating effect. Presence of functional groups like –OH or –SH may increase the chelation leading to the formation of five or six membered ring. Scheme of Schiff base formation is given in following **Fig. 1.1**.

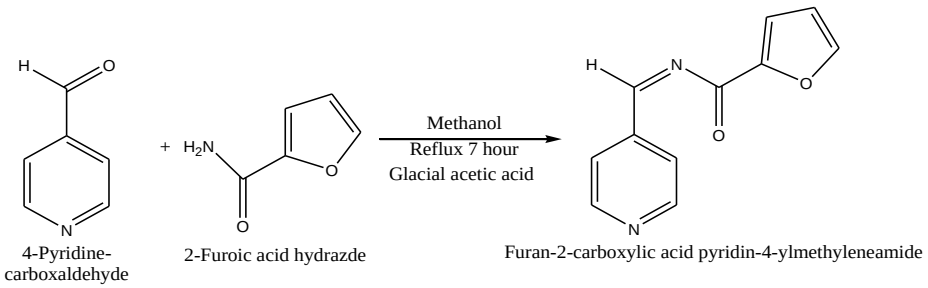


Fig. 1.1 Scheme of Schiff base formation

1.4. Schiff base metal complexes

Schiff bases are one of the most flexible and versatile group of ligands due the presence of various active donor sites they possess. This versatility has made them polydentate ligand and thus can form numerous complexes with various transition and inner transition metal ions [40]. Schiff bases and its metal complexes have a wide variety of interesting properties and applications which include catalytic, synthetic, analytical, biochemical, electrochemical sensing and therapeutic applications. Schiff bases have high affinity for chelation with transition metal ions. The stability of metal complexes depends on chelating effect. The presence of chelating agents like carbonyl, hydroxyl or thio groups close to the proximity of azomethine (C=N) linkage increases the chelation and thus stability of metal complexes. Schiff base and its metal complexes are thus of recent research interest comprising of various research fields such as organometallic, inorganic, bioinorganic, catalytic and electrochemical [112-113]. In our present work we focus on oxygen, nitrogen and sulphur containing ligands and their transition metal complexes of nickel and copper metal ions. Some examples of Schiff base metal complexes containing nitrogen, oxygen and sulphur donor atoms are given the following **Fig. 1.2**.

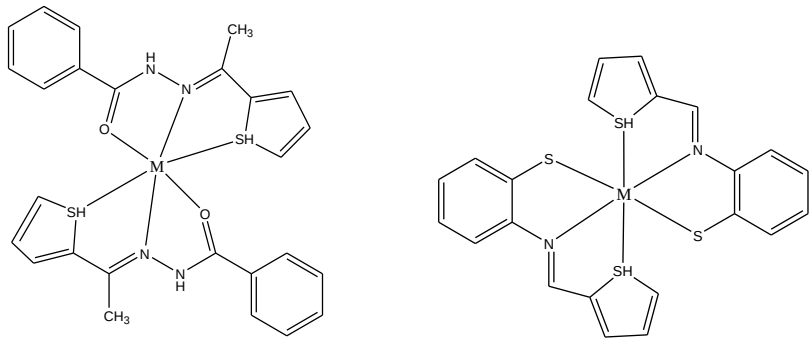


Fig. 1.2 Schiff base metal complexes

1.3 Synthesis of Schiff bases and their metal complexes

The Schiff base metal complexes are synthesized by two ways, template synthesis and the other one is conventional method.

1.3.1 Conventional method

In conventional method the ligand is synthesized prior and then the metal salt is added to the synthesized ligand to form the complex.

Synthesis of the ligand and metal complex

A general scheme for synthesis of the ligand and metal complex is given in **Fig. 1.3** and **Fig. 1.4**.

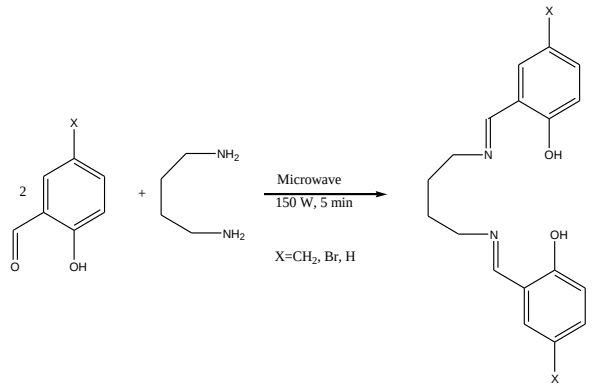


Fig. 1.3 Scheme of synthesis of ligand

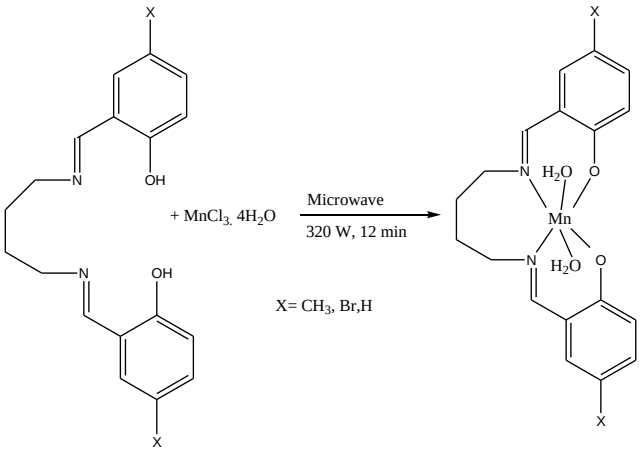


Fig. 1.4 Scheme for the synthesis of Schiff base metal complexes

1.3.2 Template synthesis

Template synthesis is a single step synthesis of metal complexes, i.e., without the isolation and purification of the ligand, the complex is synthesized. It is an in situ reaction [41] [43]. The condenstion of carbonyl compund and amine, and the coordination of metal takesplace in a single step reaction [114]. Template can be defined as “any species that organizes an assembly of molecular building blocks by non-covalent interraction favouring of a specific

product" [121]. Template synthesis is a useful technique to achieve the synthsis of assemblies that have unusal topologies such as macrocycles, rotaxanes, helicates and catananes [115].

Template synthsis can be carried out in several ways, thermodynamic, microwave irradiation and ultrasonication method. In thermodynamic processes, one of the reactants binds the template and an equilibirium is formed. This equilibirium is shifted towards the formation of a specific product. Microwave irradiation is an irreversible process leading to the formation of wanted product. In this case the reaction can be very fast and shorter time with high yield. A general scheme for the template synthsis is given in **Fig. 1.5**.

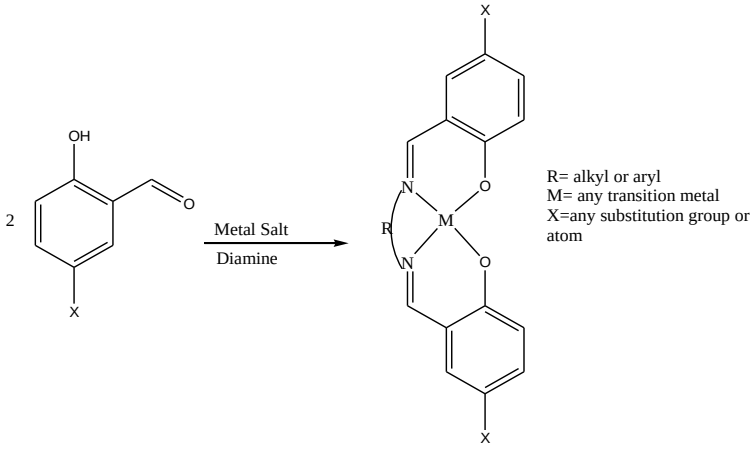


Fig. 1.5 Scheme of Template synthesis of Schiff base metal complexes

1.8 The role of metal ions in biological systems

Life has evolved from inorganic materials and thus inorganic chemistry is vital to all biological processes. Though many biological reactions are already known most of the things are yet to be exposed. Inorganic chemistry is an interdisciplinary science and it covers different areas like biochemistry, biology, physiology, medicine, agriculture, physics, and environmental sciences. All the biological activities are mediated by specific proteins or enzymes, most of which require one or more metal ions for their activity and their structural integrity. Enzymes bound metal ions, by virtue of their unique coordination chemistry, may provide binding sites of the substrates confer and stabilize the appropriate conformation of the enzymes and may function as catalytic centers. Lability and inertness of metal ligand bonds, stereochemistry, stability, magnetic and redox properties of metal ligand complexes manifest themselves in all the reactions of metal ions in metalloproteins and metalloenzymes.

1.9 Biological importance of nickel, copper and its complexes

Nickel and copper are considered as essential elements in animals, microorganisms and plants and it is a constituent of many of the enzymes and proteins [116]. Nickel is found in a number of groups of bacteria. It is an essential element in the biosynthesis of the hydrogenase and carbon monoxide dehydrogenase. Several plant species also contain nickel containing protein. Urease from jack beans is rich in nickel protein. It is a constituent part of all organs of vertebrates. Nickel deficiency may cause reduced growth, histological change, reduced resorption, anaemia and thus vital to metabolism and life [117-118].

Many of the proteins contain copper ions. They are involved in many biological processes such as electron transfer and oxidation- reduction of various organic moieties. In fact copper containing proteins acts as redox catalysts. Dicopper proteins are involved in hydroxylation, one electron oxidation of pseudo azurine/one electron reduction of NO_2^-.

Schiff bases have excellent therapeutic properties. Its medicinal property can be enhanced by coordination with metal ions. Copper and nickel complexes have several biological applications including antibacterial, antifungal, antiviral, analgesic antitumour etc. So these metals can be utilized for combating diseases of human body.

1.6 Antimicrobial properties of ligands and their metal complexes

The characteristic properties of coordination compounds depends on the nature of donor atom, steric factors, nature of the metal ion, structure of the coordinating ligand, the metal-ligand interaction and the nature of the solvent employed [50-51]. Schiff bases show excellent biological activities against many pathogenic bacteria, fungi and against certain cancerous cells [34] [48-49]. Schiff bases having chelative donor sites like nitrogen, oxygen and sulphur when coordinated to metal ions an enhanced biological activity is observed [9] [50] [52]. Factors controlling antimicrobial activities are the following,

7. Chelation
8. Cell permeability and
9. Lipophilicity

Generally metal chelates have enhanced activity than the free ligand [14] [56-57]. As chelation increases biological activity also increases [9] [50] [52] because chelation increases

the cell permeability. On chelation the polarity of the metal ion reduces and the lipophilic nature of the metal ion enhances [7] [37] [53]. This enhanced lipophilic nature favours cell permeability. Thus metal atoms can permeate more effectively through the lipid layer of microbes destroying them or blocking their active sites [28] [30] [51-52]. Thus one of the ways to improve the biological activity is to increase the number of chelate rings [9] [37] [53-54].

1.7 Objectives of the study

- To synthesize ligands containng sulphur, nitrogen and oxygen
- To synthesize metal complexes of copper and nickel using the synthesized ligands
- To characterize the synthesized ligands and metal complexes
- To conduct antimicrobial studies of the synthesized ligands and metal complexes

Conclusion

Even though advanced modern science and technology hails for its invention and innovation to control the infectious diseases, microbial resistance to antibiotics is a severe issue to be confronted and solved [9] [28] [48] [50] [63]. Thus inorganic chemistry opens a new way for new research and development.

Chapter 2

Review of Literature

There have been numerous studies on the physicochemical properties and mode of coordination of transition metal complexes containing Schiff base ligands. These Schiff base metal complexes have attracted considerable attraction due to their antimicrobial activity. This chapter enumerates the literature survey on synthesis, characterization and antimicrobial studies of nitrogen, oxygen and sulphur containing ligands and their transition metal complexes.

Antimicrobial activity of metal Schiff base complexes

Mohammad Shakir and co-workers have reported the synthesis, characterization and evaluation of complexes of La^{3+}, Nd^{3+}, Pr^{3+}, Gd^{3+} and Er^{3+} from N, N'-bis-(2-thiophenecarboxaldimine)-3,3–diaminobenzidene (**Fig. 2.1**). Spectral studies reveal the coordination of ligand with metal ions through the free amino group and the azomethine nitrogen. The complexes and the Schiff base ligand has been studied for their anticancer activity towards cervical and breast cancer cell lines. The complexes exhibited greater activity than the Schiff base [68].

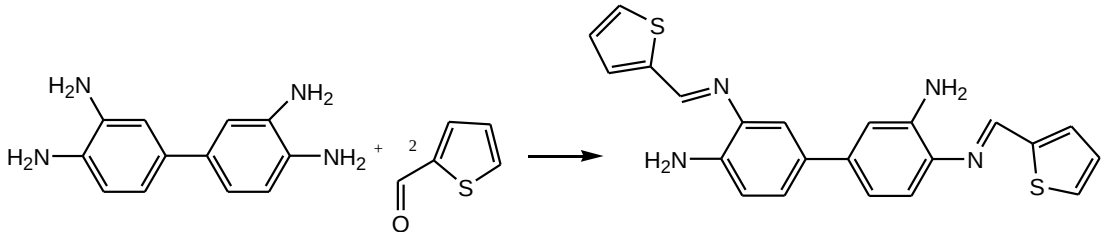


Fig. 2.1 Formation of the Schiff base ligand

A novel hydrazone Schiff base ligand was synthesized by reacting 2-furoic acid hydrazide with terephthalaldehyde and its binuclear complexes of Co(II), Ni(II), Cu(II) and Zn(II) were also synthesized (**Fig. 2.2**). The hydrazone Schiff base, Furo-(phenyldimethine)-carbohydrazone, acts as tetradentate ligand. The complexes exhibited an octahedral geometry and are non electrolytic in nature. The hydrazone ligand and its Zn(II) complex have been screened for their in vitro antimicrobial activities and the complexes show enhanced activity than the free ligand [40].

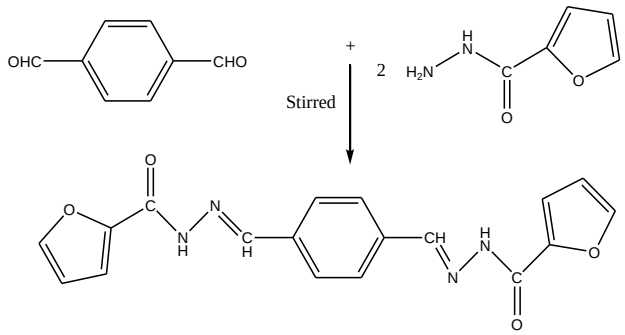


Fig. 2.2 Synthesis of the hydrazone Schiff base ligand

Parveez Gull and Athar Adi Hashni have reported the synthesis of a macrocyclic ligand from pentane-2,4-dione and 1, 4-dicarbonylphenyl-dihydrazide, and its Co(II), Cu(II) and Ni(II) complexes (**Fig. 2.3**). The macrocyclic ligand and its mononuclear non electrolytic complexes have been tested for their antimicrobial activities and it was found that the complexes exhibited more activity than the macrocyclic ligand [31].

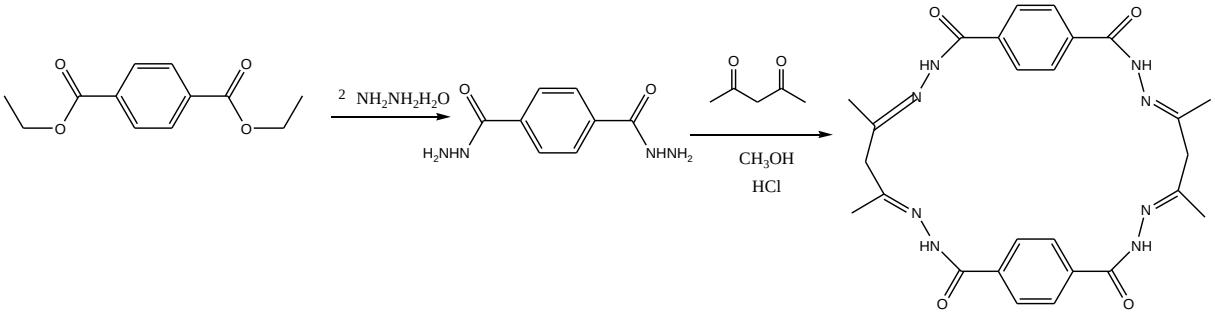


Fig. 2.3 Synthesis of the macrocyclic ligand

Hatice Yildirim *et al*., synthesized and characterized Ru(II) complexes from the reaction of $[Ru(H)(Cl)(CO)(PPh_3)]$ and $[\{(\eta^6\text{-p-cymene})RuCl\}_2(\mu\text{-}Cl)_2]$ with thiophene-2-carboxaldehyde thiosemicarbazone (**Fig. 2.4**). The antimicrobial activities of the complexes were tested and the test complexes are inactive towards the selected Gram-negative bacteria and fungus whereas the complexes exhibited moderate activity towards Gram-positive bacteria [10].

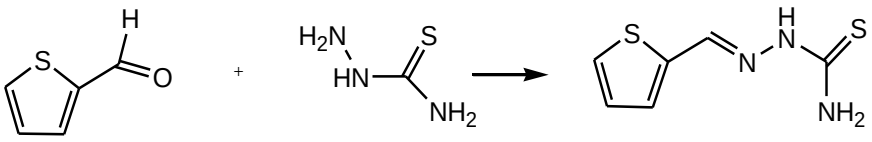


Fig. 2.4 Synthesis of thiophene-2-carboxaldehyde thiosemicarbazone ligand

Mahasin Elias and co-workers have reported the synthesis and characterization of Schiff base derived from potassium 2-N (4N,N-dimethylaminobenzyliden)-4-trithiocarbonate 1,3,4-thiadiazole and its Co(II), Ni(II), and Cu(II) complexes (**Fig. 2.5**). The ligand and its six-coordinated octahedral complexes were screened for their antibacterial inhibition against Pseudomonas aeruginosa and Staphylococcus aureus. The Ni(II) complex exhibited greater antibacterial activity towards the bacterial strains than the free ligand and other complexes [74].

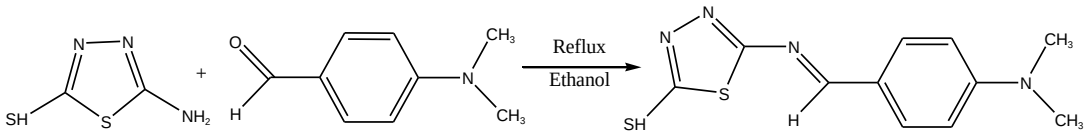


Fig. 2.5 Synthesis of the Schiff base ligand

Mohammad Nasir Uddin and co-workers have reported the synthesis and characterization of a novel Schiff base derived from the condensation reaction of 2-thiophenecarboxaldehyde with 2-aminothiophenol and propane-1,2-diamine and their complexes of Ni(II), Cu(II) and Zn(II) (**Fig. 2.6)**. The Schiff base and its non-electrolytic octahedral complexes have been evaluated for their antibacterial activity against four human pathogenic bacteria and metal complexes exhibited greater antibacterial activity compared to its free ligand [84].

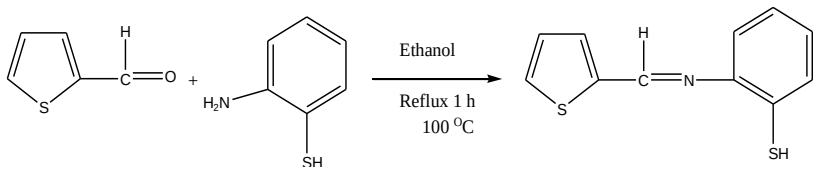


Fig. 2.6 Synthesis of the thiophene ligand

Salman M. Saadeh has reported the synthesis and characterization of a trifunctional SNO-donor system ligand, 2-acetylthiophene benzoylhydrazone and its complexes of Co(II), Ni(II), Cu(II) and Zn(II) (**Fig. 2.7**). The Schiff base ligand and its complexes were screened for their antibacterial activity and they are inactive on the standard bacterial strains used in the study [85].

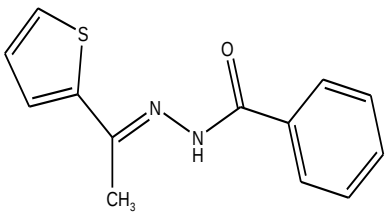


Fig. 2.7 Structure of the trifunctional ligand

Mishra A. P. *et al*., synthesized and characterized two Schiff bases from 2-thiophene-carboxaldehyde with 2-chloro-4-nitroaniline (TCA) and 2-imidodicarbonic diamide (TID) (**Fig. 2.8**) and its metal complexes of Cu(II), Ni(II) and Co(II). The Schiff base and metal complexes show an increased antimicrobial activity against the selected test bacteria and fungus. The metal complexes exhibited better antimicrobial property than the Schiff bases [87].

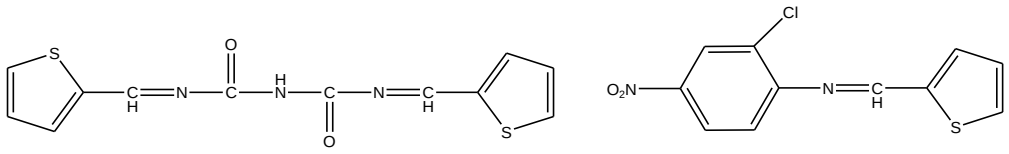


Fig. 2.8 Structure of the Schiff bases

Cezar Spinu *et al*., have reported the synthesis and characterization of metal complexes of Fe(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) from novel Schiff base ligand derived by the condensation reaction of 2-thiophenecarboxaldehyde with N-(2thienylmethylidene)-2-aminopyridine and 2-aminopyridine (**Fig. 2.9**). The Schiff base, the octahedral Fe(II), Co(II), Ni(II), and Cu(II) complexes, and the tetrahedral Zn(II) and Cd(II) complexes have been evaluated for their antibacterial activity against some selected microbes [89].

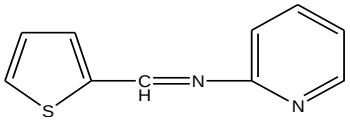


Fig. 2.9 Structure of the ligand

P. Venkateswara Rao and co-workers have synthesized and characterized a novel Schiff base ligand formed from 4-nitropyridine and 4-pyridine carboxaldehyde in the presence dilute acid and iron powder (**Fig. 2.10**). The Schiff base and its complexes show good antimicrobial activity against selected test bacteria and fungi. The metal complexes are good inhibitory agents than the ligand [104].

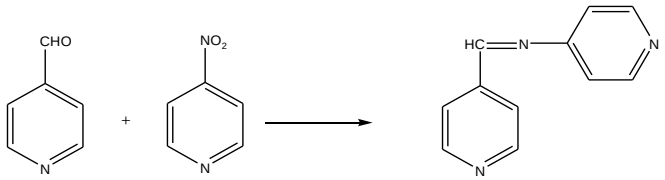


Fig. 2.10 Synthesis of the ligand

Sheeja Lovely and M. Christudhas have synthesized and characterized a novel Schiff base ligand, 4-pyridine carboxaldehyde 3-amino pyridine and its complexes of Co(II), Ni(II) and Cu(II) (**Fig. 2.11**). Moderate antimicrobial activity has been observed for both ligand and complexes [119].

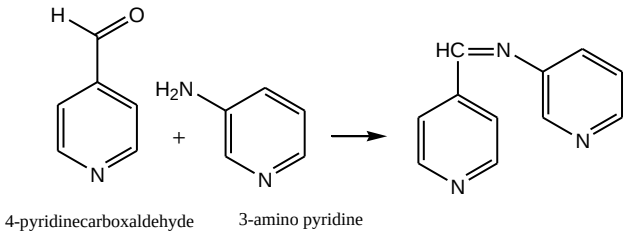


Fig. 2.11 Structure of the ligand

Azadeh Tadjarodi and Salman Najjari have used microwave irradiation technique to synthesize a new Cd(II) complex of dichloro 4- pyridinecarboxaldehyde thiosemicarbazone and characterized (**Fig. 2.12**). Both the ligand and complex have been evaluated for their microbial inhibitory activity [120].

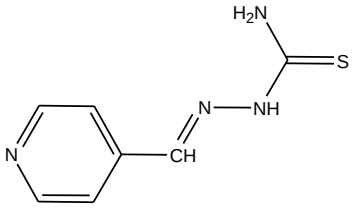


Fig. 2.12 Structure of the ligand

Conclusion

Numerous studies have done on the antimicrobial activities of Schiff base ligands containing nitrogen, oxygen and sulphur donor atoms and their metal complexes. Literature survey reveals that Schiff base ligands and their transition metal complexes are biologically active towards many pathogenic bacteria and fungi and thus they are antimicrobial agents. Coordination of a metal to the ligand, in most cases, increases the biological activity and it can be explained on the basis of Chelation theory. The Schiff bases show moderate to good antimicrobial activity compared to their metal complexes and standard drugs.

Chapter 3

Experimental

3.1 Physico-chemical characterization of ligands and complexes

UV-visible, CHNS, FT-IR, ^{1}HNMR, EPR and molar conductivity measurements have been employed in the present study with a view to correlate the physical and chemical properties of the ligands and metal complexes. The procedures of various characterization techniques are discussed in the following section.

3.1.1 Elemental analysis

The analysis of percentage of elements C, H, N and S in the ligands and complexes were carried out on Elementar Vario EL III CHNS analyzer at SAIF, Kochi.

3.1.2 UV-visible spectroscopy

Electronic absorption spectra of the ligands and their copper and nickel complexes in the solution phase were recorded in the region of 200-900 nm on the Perkin Elmer Lambda UV-visible spectrophotometer. The UV-visible Spectroscopy is a useful tool to predict the electronic transition of the complexes and d-d transition of the copper metal ion. From these spectra we know the electronic configuration of the metal ion and the magnetic moment of the metal complexes. The spectra were recorded as absorbance against wavelength.

3.1.3 Fourier-Transform Infrared (FT-IR) spectroscopy

FT-IR spectroscopy can be used to investigate the structural features of ligands and their copper and nickel complexes. The spectra were recorded on a Bruker 360 FT-IR spectrophotometer using KBr pellet technique in the range 4000-400 cm^{-1}. The spectra were recorded as % transmittance against wavenumbers (cm^{-1}).

3.1.4 ^{1}H NMR Spectroscopy

^{1}H NMR spectra of the ligands were recorded using Bruker AMX 400 FT-NMR Spectrometer using DMSO as solvent at Anthem Biosciences, Bangalore.

3.1.5 Molar conductivity measurements

Molar conductivity measurements of complexes in acetonitrile and DMF (10^{-3}M) were measured at room temperature using direct reading digital conductivity meter.

3.1.6 Electron paramagnetic resonance (EPR) spectroscopy

The EPR spectra were recorded on JES-FA 200 spectrometer at SAIF, IIT Madras using diphenylpicrylhydrazine (DPPH) as the reference. EPR spectra were taken for the copper complexes. All the spectra were run in DMSO solution at liquid nitrogen temperature (LNT) and at room temperature (RT).

3.1.7 Antimicrobial studies by Zone Inhibition method

Determination of antibacterial activity

100 micro litre of the test culture was inoculated on Miller Hilton agar plates (90 mm) and prepared bacterial cultures. All the test compounds, standards and vehicle control were impregnated on inoculated plates. These bacterial plates were incubated at 35 ^{0} C for 24-48 hours. The plates were observed for Zone Inhibition around the well.

Determination of antifungal activity

100 micro litre of the test culture was inoculated on Miller Hilton agar plates (90 mm) and prepared fungal cultures. All the test compounds, standards and vehicle control were impregnated on inoculated plates. These fungal plates were incubated at room temperature for 24-48 hours. The plates were observed for Zone Inhibition around the well.

3.2 Experimental procedure

3.2.1 Chemicals and reagents

1. 4-Pyridinecarboxaldehyde
2. 2-Thiophenecarboxamide
3. 2-Furoic acid hydrazide
4. Indole-3-carboxaldehyde
5. Nickel chloride ($NiCl_2.6H_2O$)
6. Copper chloride ($CuCl_2.2H_2O$)
7. Glacial acetic acid
8. Methanol

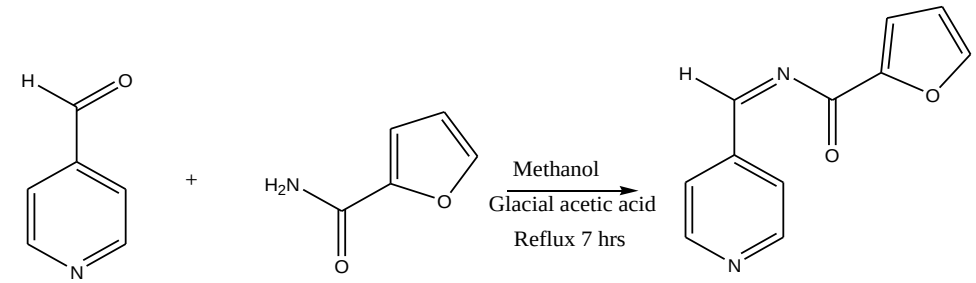
3.2.2 Synthesis of ligands

Two novel ligands were synthesized using 4-Pyridinecarboxaldehyde, 2-Thiophenecarboxamide, 2-Furoic acid hydrazide and Indole-3-carboxaldehyde. They were characterized by various physical and chemical techniques and they were used for the synthsis of copper and nickel complexes. The ligands are

1. Furan-2-carboxylic acid pyridin-4-ylmethyleneamide (L^1) and
2. Thiophene-2-carboxylic acid 1H-indol-2-ylmethyleneamide (L^2)

3.2.2.1 Synthesis of Furan-2-carboxylic acid pyridin-4-ylmethyleneamide (L^1)

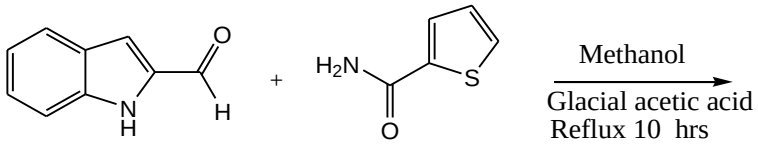
1 mmol of 2-Furoic acid hydrazide (0.126 g) was dissolved in 15 ml of methanol and to this was added 1 mmol of 4-Pyridinecarboxaldehyde (0.94 ml) followed by two drops of glacial acetic acid. The reaction mixture was refluxed for 7 hours. It was cooled to room temperature about 12 hours. On slow evaporation, pale brown crystals of Furan-2-carboxylic acid pyridin-4-ylmethyleneamide (L^1) (**Scheme 3.1**) were separated out. The crystals formed were filtered, washed with methanol and dried over P_4O_{10} under vacuo. Yield, 73%.



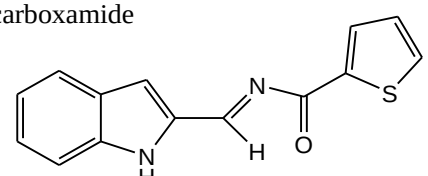
Scheme 3.1 Furan-2-carboxylic acid pyridin-4-ylmethyleneamide (L^1)

3.2.2.2 Synthesis of Thiophene-2-carboxylic acid 1H-indol-2-ylmethyleneamide (L^2)

1 mmol of Indole-3-carboxaldehyde (0.145 g) was dissolved in 10 ml methanol and to this was added 1 mmol of 2-Thiophenecarboxamide (0.127g). Two drops of glacial acetic acid were also added to the reaction mixture. The mixture was refluxed for 10 hours. It was cooled to room temperature about 12 hours. On slow evaporation, pale pink coloured substance of Thiophene-2-carboxylic acid 1H-indol-2-ylmethyleneamide (L^2) (**Scheme 3.2**) were separated out. The product formed were filtered, washed with methanol and dried over P_4O_{10} under vacuo. Yield, 75%.



Indole-3-carboxaldehyde 2-Thiophenecarboxamide



Thiophene-2-carboxylic acid 1*H*-indol-2-ylmethyleneamide

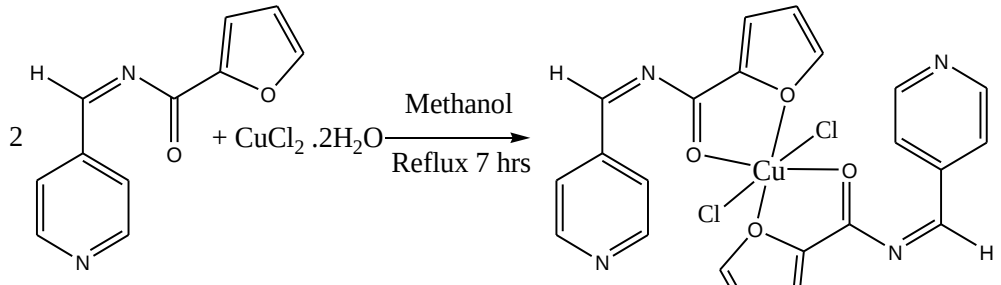
Scheme 3.2 Synthesis of Thiophene-2-carboxylic acid 1H-indol-2-ylmethyleneamide (L^2)

3.2.3 Synthesis of complexes

Copper(II) and nickel(II) complexes of the ligands Furan-2-carboxylic acid pyridin-4-ylmethyleneamide (L^1) and Thiophene-2-carboxylic acid 1H-indol-2-ylmethyleneamide (L^2) were synthesisized. They were characterised by differrent characterization techniques like elemental analysis, molar conductivity measurements, UV-vis., FT-IR and ^{1}H NMR.

3.2.3.1 Synthesis of copper complex of L^1

To a solution of 2 mmol of Furan-2-carboxylic acid pyridin-4-ylmethyleneamide (L^1) (0.200 g) in methanol, 1 mmol of copper chloride (0.170 g) dissolved in methanol was added (**Scheme 3.3**). The reaction mixture was refluxed for 7 hours. The resulting greenish yellow solution was allowed for slow evaporation at room temperature. The resulted greenish yellow precipitates were filtered, washed with methanol, recrystallized from methanol and dried under vacuo. Yield, 71%.

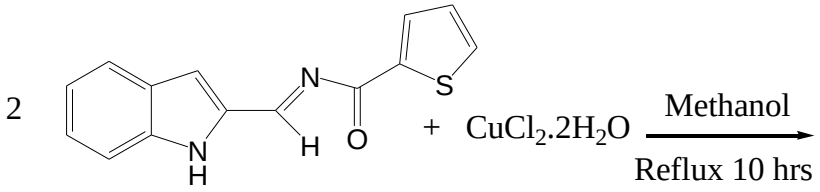


Furan-2-carboxylic acid pyridin-4-ylmethyleneamide

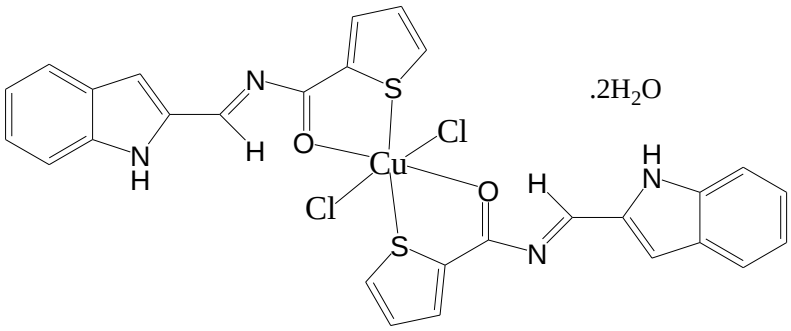
Scheme 3.3 Preparation of copper complex of L^1

3.2.3.2 Synthesis of copper complex of L^2

To a solution of 2 mmol of Thiophene-2-carboxylic acid 1H-indol-2-ylmethyleneamide (L^2) (0.253 g) in methanol, 1 mmol of copper chloride (0.170 g) dissolved in methanol was added. The mixture was refluxed for 10 hours (**Scheme 3.4**). The resulting brownish red solution was allowed to stand at room temperature for slow evaporation. The separated brownish precipitates were filtered, washed with methanol, recrystallized from methanol and dried under vacuo. Yield, 70 %.



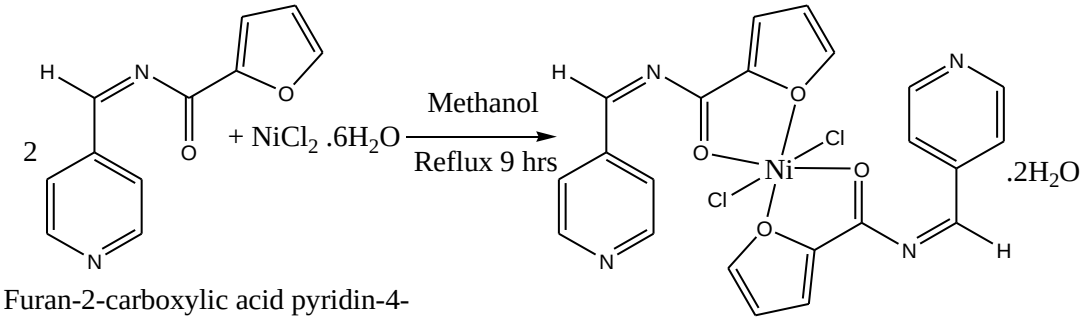
Thiophene-2-carboxylic acid 1*H*-indol-2-yl-methyleneamide



Scheme 3.4 Preparation of copper compex of L^2

3.2.3.3 Synthesis of nickel complex of L^1

To a methanolic solution of 2 mmol of Furan-2-carboxylic acid pyridin-4-ylmethyleneamide (L^1) (0.200 g), 1 mmol of nickel chloride (0.237 g) dissolved in methanol was added. The reaction mixture was refluxed for 9 hours (**Scheme 3.5**). The resulting solution was allowed to evaporate room temperature. Greenish yellow precipitates seperated were filtered, washed with methanol, recrystallized from methanol and dried under vacuo. Yield, 72%.

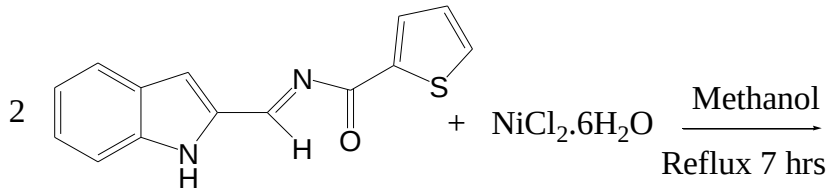


Furan-2-carboxylic acid pyridin-4-ylmethyleneamide

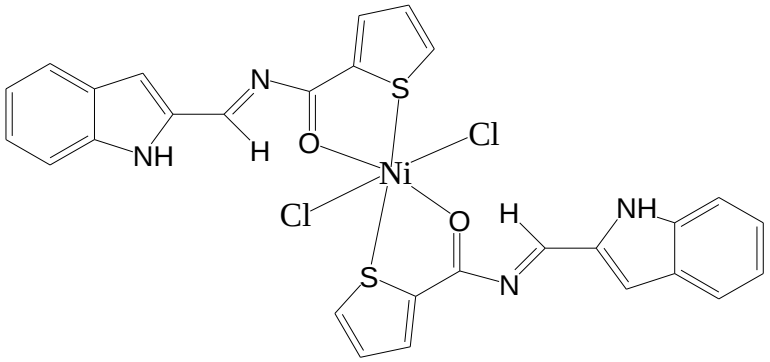
Scheme 3.5 Preparation of nickel complex L^1

3.2.3.4 Synthesis of nickel complex of L^2

To a solution of 2 mmol of Thiophene-2-carboxylic acid 1H-indol-2-ylmethyleneamide (L^2) (0.253 g) in methanol, 1 mmol of nickel chloride (0.237 g) dissolved in methanol was added. The reaction mixture was refluxed for 7 hours (**Scheme 3.6**). The resulting solution was allowed to evaporate at room temperature. The separated pale green precipitates were filtered, washed with methanol, recrystallized from methanol and dried under vacuo. Yield, 72%.



Thiophene-2-carboxylic acid 1*H*-indol-2-yl methyleneamide



Scheme 3.6 Preparation of nickel complex of L^2

Chapter 4

Results and Discussions

4.1 Physical properties and analytical data of compounds

The physical properties and analytical data of the ligands and their copper and nickel complexes are summarized in **Table 4.1**. Elemental analysis of the ligands and complexes corresponds to the suggested molecular formulae. The yield of the synthesized complexes is varied from 70 % to 75 %. The synthesized ligands and metal complexes are soluble in organic solvents like DMF, DMSO and acetonitrile.

Table 4.1 Analytical data of the ligands and their metal complexes

Compound	**Colour**	**Melting Point (^{o} C)**	**Solubility**	**Analytical data Expt. (Calc.) %**
$C_{11}H_8N_2O_2$ (L^1)	Light green	182-185	Acetonitrile DMF DMSO	C 65.86 (65.99) H 3.56 (3.98) N 13.99 (13.97)
$C_{14}H_{10}N_2OS$ (L^2)	Light pink	142-145	Ethanol Methanol Acetonitrile DMF, DMSO	C 66.11 (66.38) H 3.47 (3.58) N 11.011 (11.05) S 12.60 (12.68)
$CuCl_2L^1_2$	Light green		Acetonitrile DMF, DMSO	C 46.64 (46.89) H 3.46 (3.57) N 9.68 (9.94)
$CuCl_2L^2_2.2H_2O$	Reddish brown		Acetonitrile DMF, DMSO	C 41.89 (42.09) H 2.96 (3.02)

				N 6.89 (7.01) S 7.92 (8.02)
$NiCl_2L^1_2.2\ H_2O$	Greenish yellow		Acetonitrile DMF, DMSO	C 47.52 (47.71) H 3.54 (3.64) N 10.01 (10.11)
$NiCl_2L^2_2$	Light green		Acetonitrile DMF, DMSO	C 53.79 (53.89) H 2.87 (2.90) N 8.95 (8.97) S 10.24 (10.27)

4.2 Molar conductivity measurements

The complexes are soluble in acetonitrile, DMF and DMSO. The solutions are non-conducting. The molar conductivity measurement values in acetonitrile and DMF are compiled in **Table 4.2.**

Table 4.2 Molar conductivity ($ohm^{-1}\ cm^2\ mol^{-1}$) values of 10^{-3} M solutions of the complexes in DMF and acetonitrile

Complex	**$CuCl_2L^1_2$**	**$CuCl_2L^2_2.2H_2O$**	**Ni $Cl_2L^1_2.2H_2O$**	**$NiCl_2L^2_2$**
Acetonitrile	14.9	14.6	15.2	15.4
DMF	19.7	16.5	19.5	17.1

4.3 FT-IR spectral studies

4.3.1 FT-IR spectra of ligands

The significant FT-IR spectra of the ligands show various bands in the region of 400-4000 cm^{-1}, and their assignments were tentatively used to establish the mode of coordination. The FT-IR spectra of the ligands are shown in **Fig. 4.1** and **4.2** and the corresponding vibrational stretching frequencies (cm^{-1}) of ligands are given in **Table 4.3.**

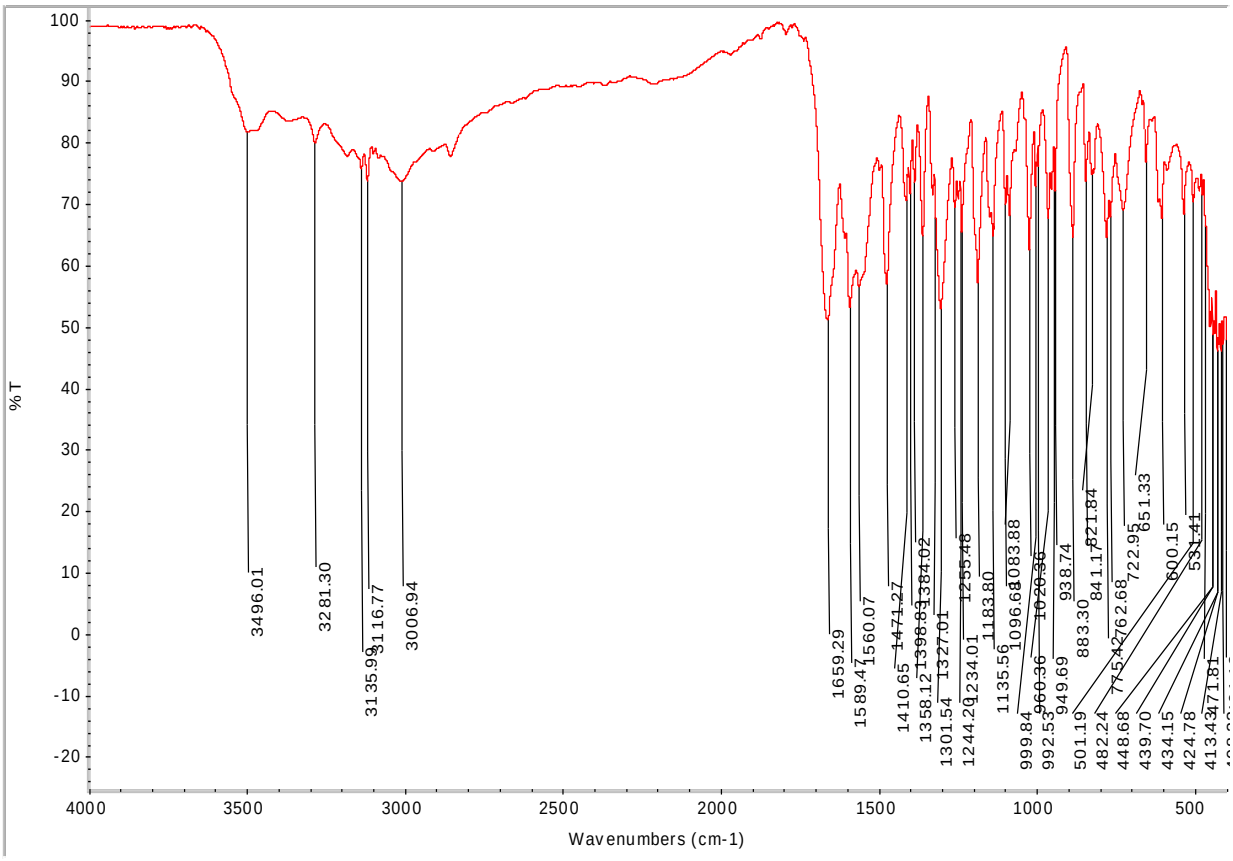


Fig.4.1 FT-IR spectrum of L^1

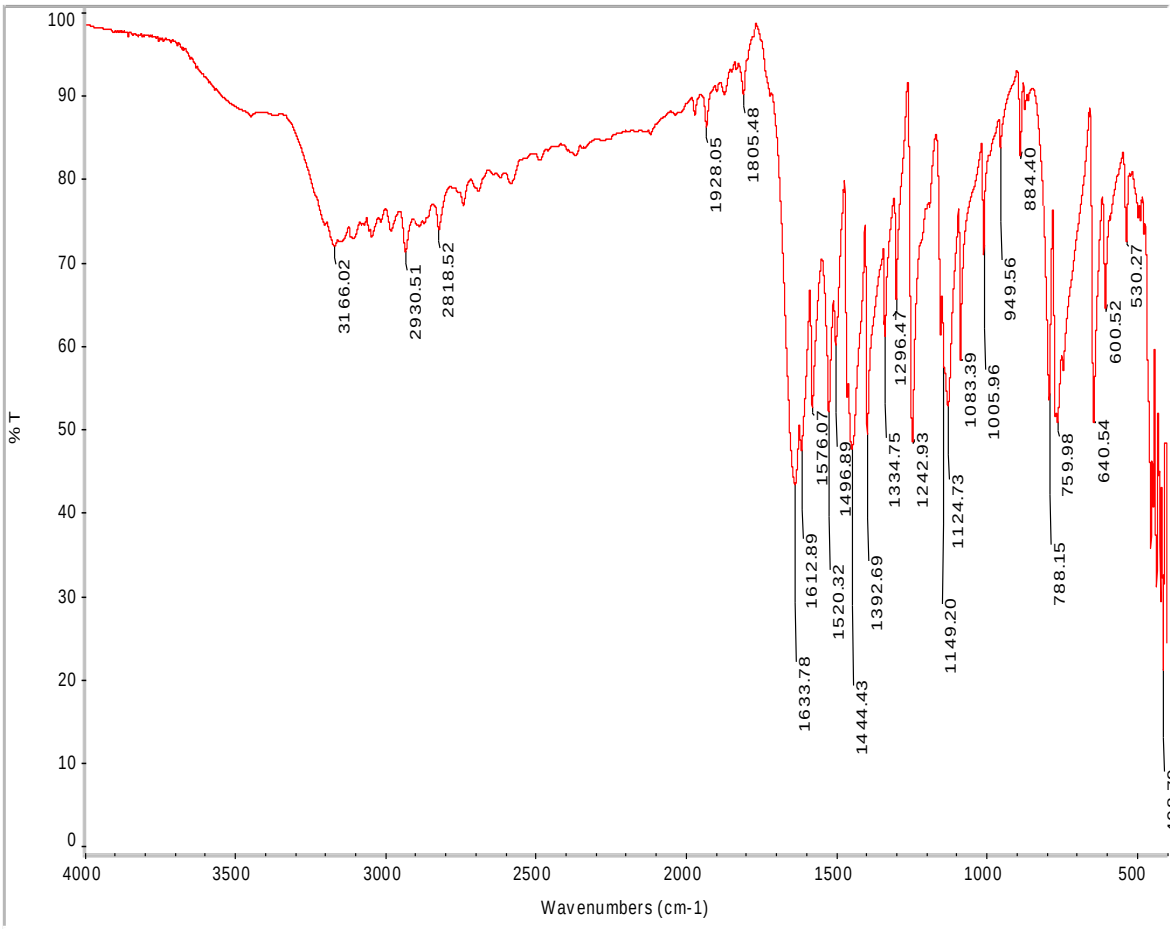


Fig. 4.2 FT-IR spectrum of L^2

Table 4.3 Important FT-IR frequencies of the ligands ν (cm^{-1})

Compound	C-O	C=O	C=N	N-H	C-S	C-S-C
$C_{11}H_8N_2O_2$ (L^1)	1244	1659	1560	-----	-----	-----
$C_{14}H_{10}N_2OS$ (L^2)	-----	1633	1576	3166	756	949

4.3.2 FT-IR spectra of complexes

4.3.2.1 FT-IR spectra of copper and nickel complexes of L^1

The significant IR spectra of the copper and nickel complexes show various bands in the region of 400-4000 cm^{-1}, and their assignments were tentatively used to establish the mode of coordination. The spectral data indicate ligand coordination to the metal. A strong sharp band observed at 1244 cm^{-1} corresponds to the C-O group of the ligand which is lowered to 1231 and 1220 cm^{-1} in complexes of copper and nickel respectively. Ligand coordination was also substantiated by the lowering of C=O appeared at 1659 cm^{-1} in ligand to 1618 cm^{-1} in complexes. Coordination of the ligand was further confirmed by the appearance of bands at 536 cm^{-1} corresponding to Cu–O and Ni–O. A sharp band observed at 3381 cm^{-1} in nickel complex shows the presence of lattice water. The FT-IR spectrum of the copper Schiff base complex is shown in **Fig. 4.3,** nickel complex is in **Fig. 4.4** and the corresponding vibrational stretching frequencies of the copper and nickel complexes are given in **Table 4.4.**

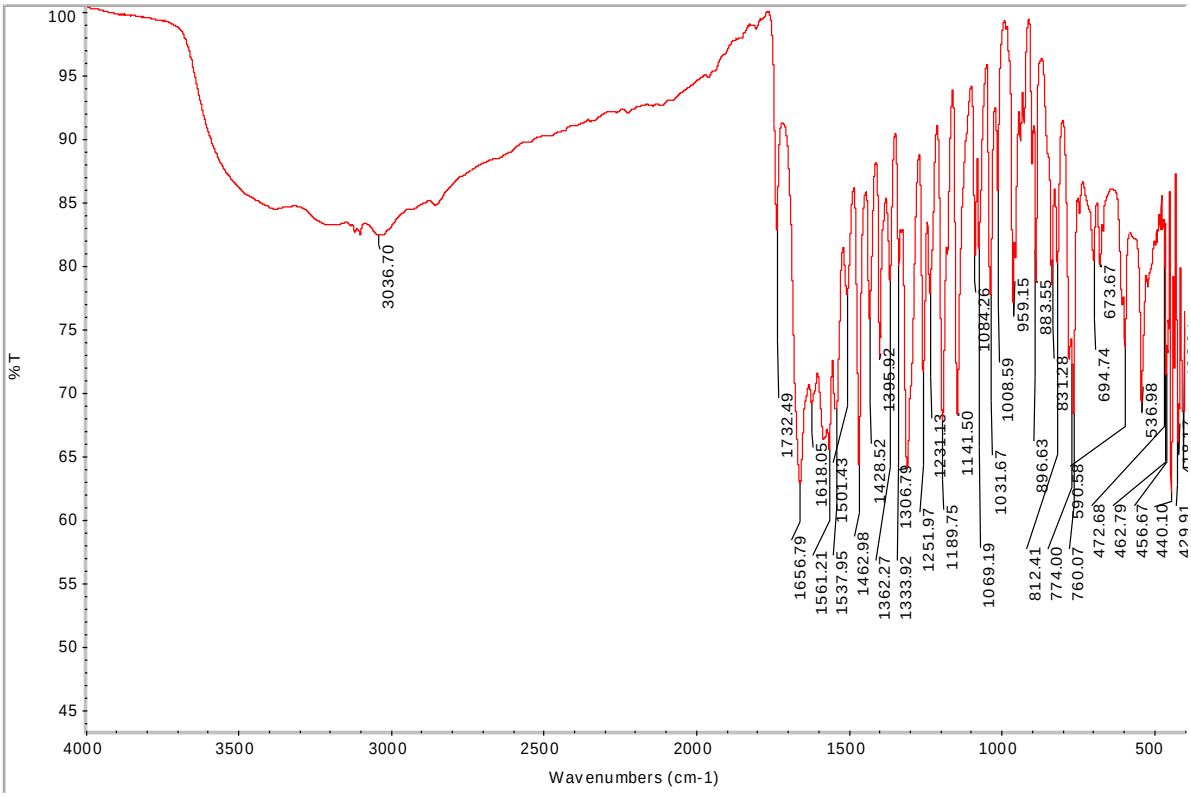


Fig.4.3 FT-IR spectrum of copper complex of L^1

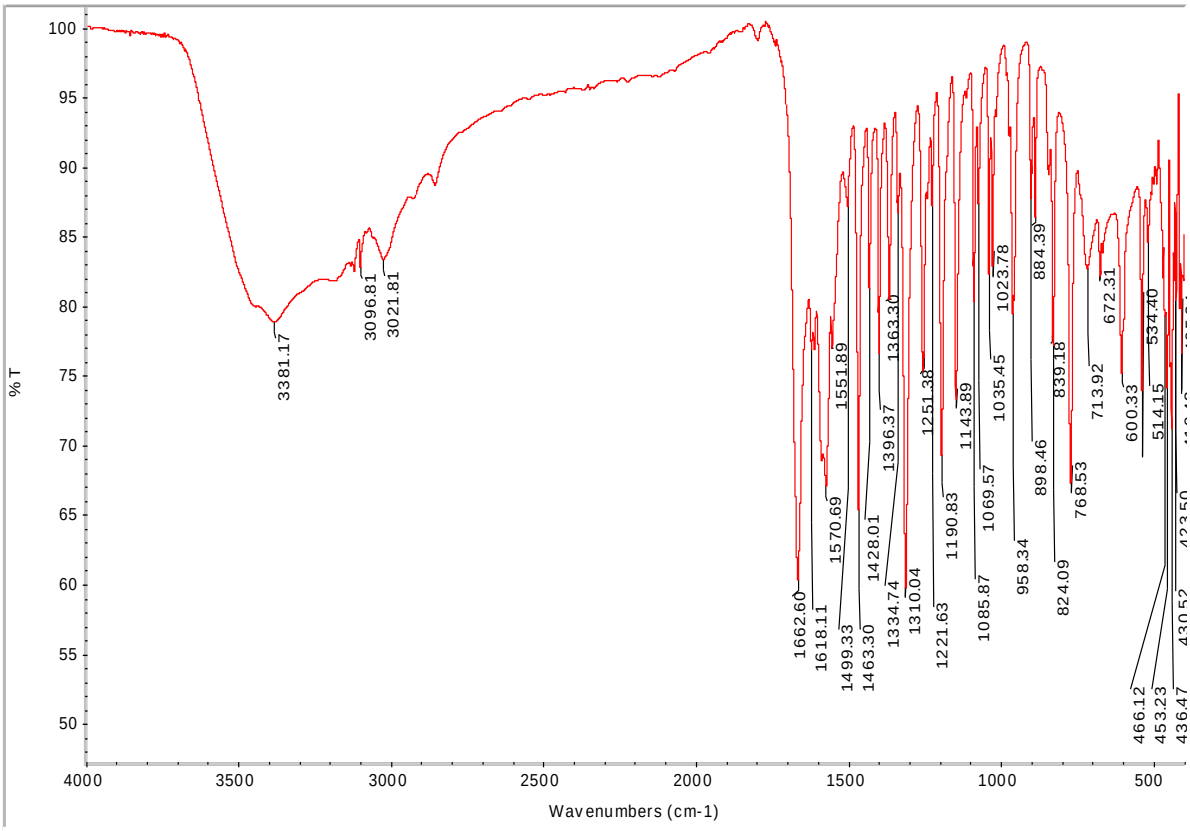


Fig.4.4 FT-IR spectrum of nickel complex of L^1

Table 4.4 Important FT-IR frequencies of the complexes of L^1 ν (cm^{-1}).

Compound	**C=O**	**C=N**	**C=C**	**M-O**	**C-O**	**H_2O**
L^1	1659	1560	1473	-----	1244	-----
$CuCl_2L^1_2$	1618	1561	1463	536	1231	-----
$NiCl_2L^1_2.2\ H_2O$	1618	1551	1462	536	1220	3381

4.3.2.2 FT-IR spectra of copper and nickel complexes of L^2

The significant IR spectra of the copper and nickel complexes show various bands in the region of 400-4000 cm^{-1}, and their assignments were tentatively used to establish the mode of coordination. The ligands are having capability to form coordinate bonds with many metal ions through both oxygen of the amide and sulphur of thiophene ring, in tetradentate mode towards the copper and nickel metal ion. The spectral data indicate the coordination of ligand to the metal. Sharp bands observed at 1612 and 1602 cm^{-1} for nickel and copper complexes respectively, corresponds to the C=O group of the coordinated ligand. Coordination of the ligand was also substantiated by the absence of vibrational stretching frequency of C-S-C in complexes which should be appeared around 949 cm^{-1}. N-H stretching frequency in ligand and complexes remain unchanged. Coordination of the Schiff base ligand was further confirmed by the appearance of bands at 536 and 530 cm^{-1} corresponding to Cu–O and Ni–O respectively. Coordination of ligand to the metal is also confirmed by the presence of new bands at 457 and 460 cm^{-1} for copper and nickel complexes respectively. A sharp band observed at 3357 cm^{-1} shows the presence of lattice water for copper complex. The FT-IR Spectrum of the copper complex is shown in **Fig. 4.5,** nickel complex is in **Fig. 4.6** and the corresponding vibrational stretching frequencies of the complexes are given in **Table 4.5.**

Table 4.5 Important FT-IR frequencies of the complexes L^2 **ν (**cm^{-1}**)**

Compound	**C=O**	**C=N**	**C=C**	**N-H**	**C-S-C**	**M- CSC**	**M-O**	**H_2O**
L^2	1633	1576	1520	3166	949	-----	-----	-----
$CuCl_2L^2_2.2\ H_2O$	1602	1576	1521	3166	----	457	536	3357
$NiCl_2L^2_2$	1612	1576	1521	3167	----	460	530	-----

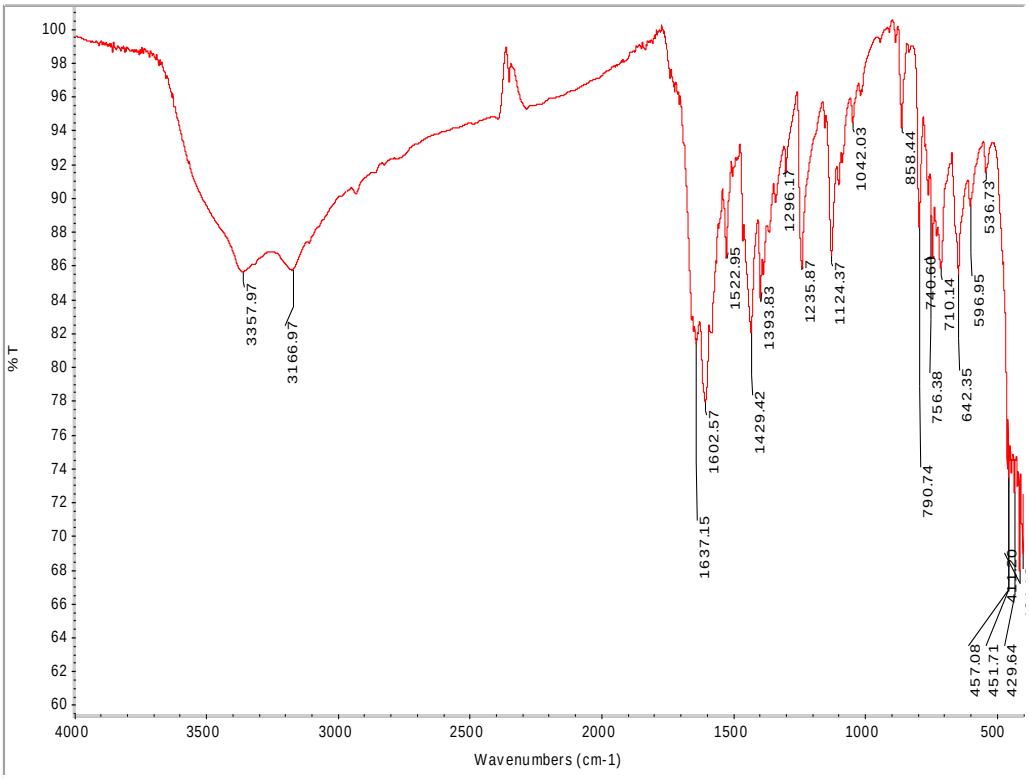


Fig.4.5 FT-IR spectrum of copper complex of L^2

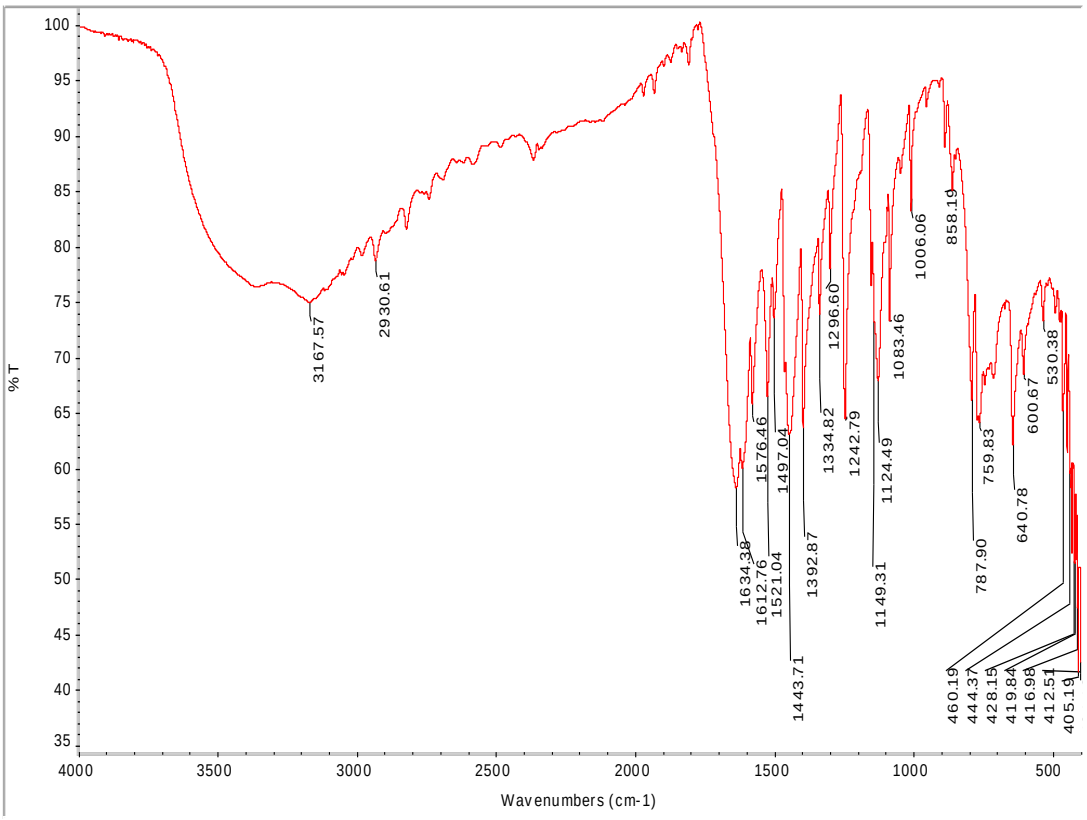


Fig.4.6 FT-IR spectrum of nickel complex of L^2

4.4 ^{1}H NMR studies

4.4.1 ^{1}H NMR spectral studies of L^{1}

The proton NMR spectrum of L^{1} recorded in DMSO (**Fig. 4.7**) displayed a singlet at δ 12.1 ppm which is assigned to azomethine proton. The peaks due to protons on furan and pyridine rings are in the range δ, 6.7 to 8.6 ppm (**Table 4.6**).

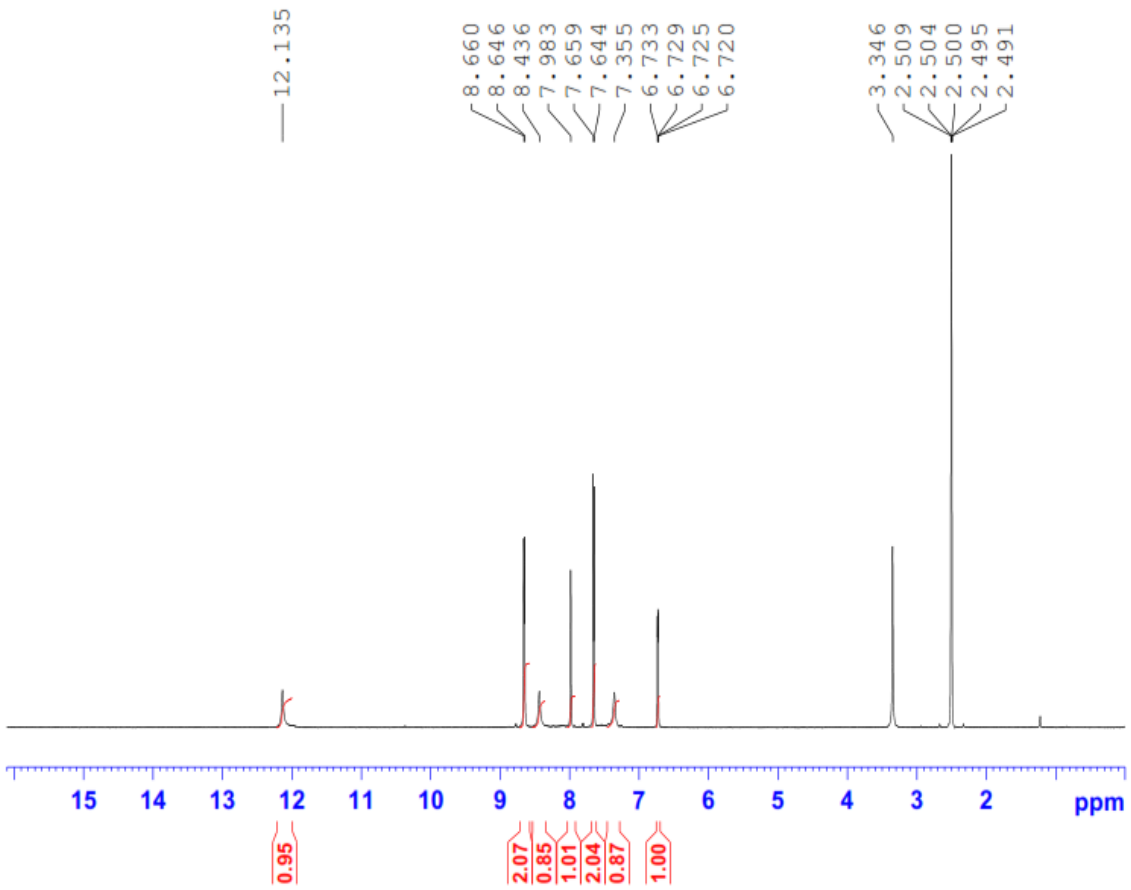


Fig. 4.7 ^{1}H NMR spectrum of L^{1}

4.4.2 ^{1}H NMR spectral studies of L^{2}

The proton NMR spectrum of L^{2} recorded in DMSO (**Fig. 4.8**) displayed a singlet at δ 9.9 ppm which is attributed to the indole NH proton. A signal at δ 12.1 ppm is ascribed to the azomethine proton (**Table 4.6**). The resonance due to protons on thiophene and benzene rings are in the range δ 7.1 to 8.2 ppm.

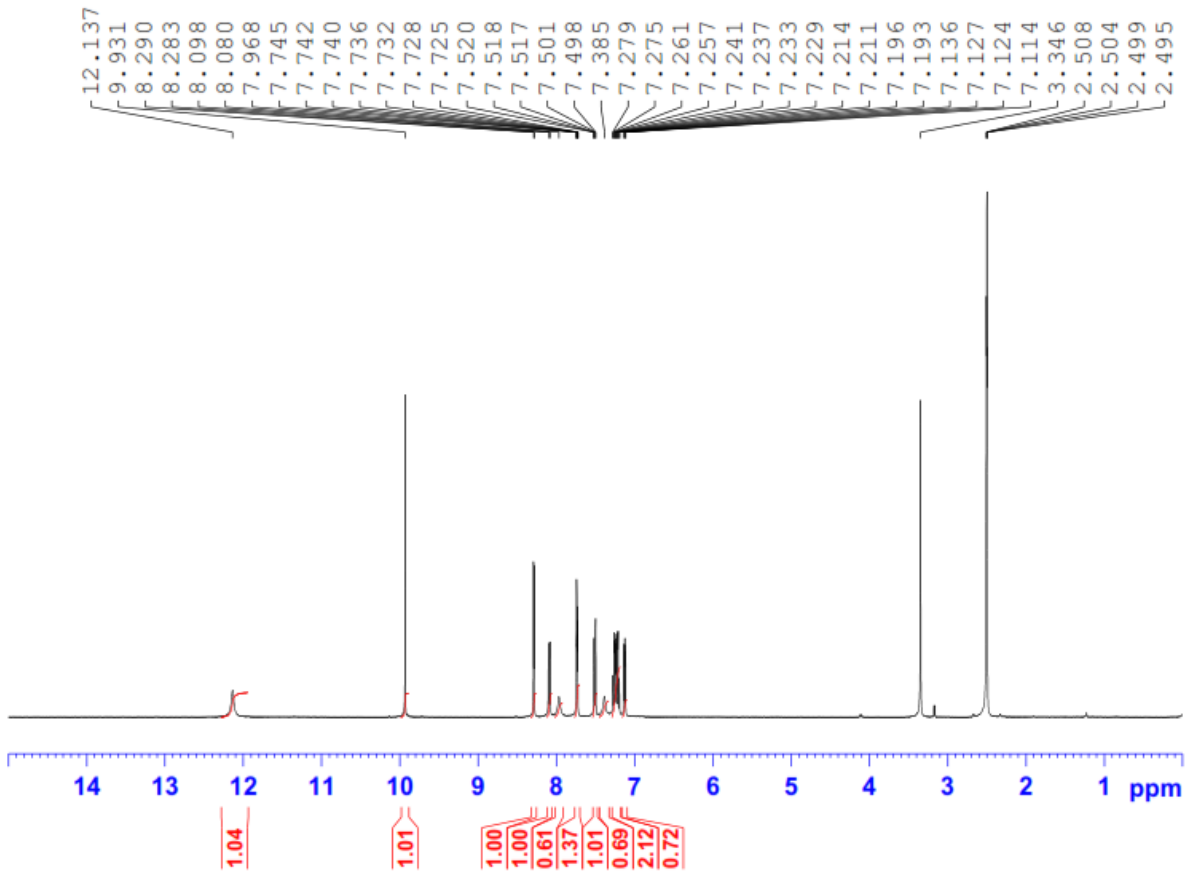


Fig. 4.8 ^{1}H NMR spectrum of L^{2}

Table 4.6 ^{1}H NMR chemical (δ in ppm) shifts for ligands

Compound	H-C=N	N-H	Ar-H
L^{1}	8.4	----	7.3-8.6
L^{2}	8.2	9.9	7.1-8.0

4.5 Electronic spectral analysis

4.5.1 Electronic absorption spectra of ligands

The electronic spectra of the ligands were recorded in the range of 200-900 nm in acetonitrile solution (10^{-5} M). UV-vis. spectra of the ligand L^1 displayed a band at 303 nm (**Fig. 4.9)** which is assigned to π- π* transition and displayed bands for L^2 at 249 and 273 nm (**Fig. 4.10**) which are assigned to n-π* and π-π* transitions respectively (**Table 4.7**).

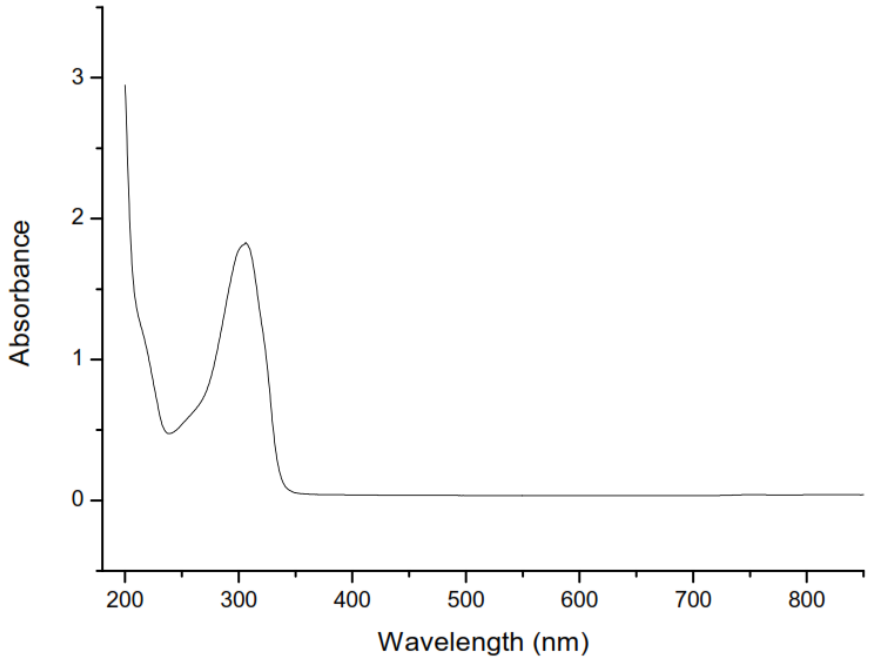


Fig. 4.9 Electronic absorption spectrum of L^1

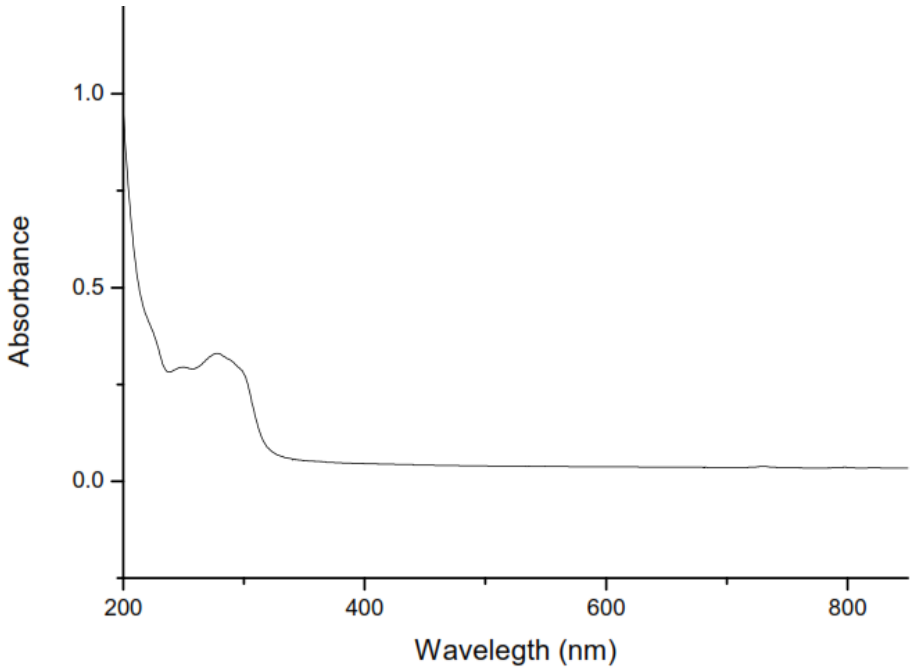


Fig. 4.10 Electronic absorption spectrum of L^2

Table 4.7 UV-vis. spectral data of ligands

Compound	**λ (ν) n-π* transitions**	**λ(ν) π-π*transitions**
L^1		303 nm (34126 cm^{-1})
L^2	249 nm (40160 cm^{-1})	279 nm (35482 cm^{-1})

4.5.2 Electronic absorption spectra of complexes

4.5.2.1 Electronic absorption spectra of copper complexes

The electronic spectra of the complexes were recorded in the range of 200-900 nm in acetonitrile solution (10^{-5} M). UV-vis. spectra of the copper complex of L^1 displayed bands (**Fig. 4.11)** at 223, 293 and 458 nm which are assigned to n-π*, π-π* and d-d transitions

respectively and copper complex of L^2 displayed bands (**Fig. 4.12**) at 243 and 466 which are assigned to π-π* and d-d transitions respectively (**Table 4.8**).

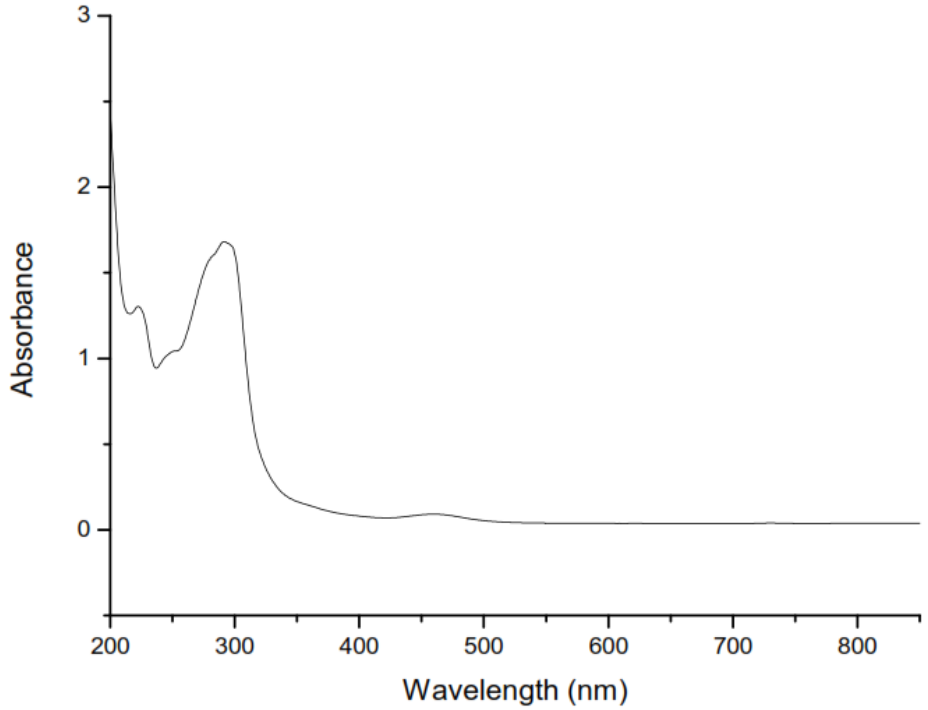


Fig. 4.11 Electronic absorption spectrum of copper complex of L^1

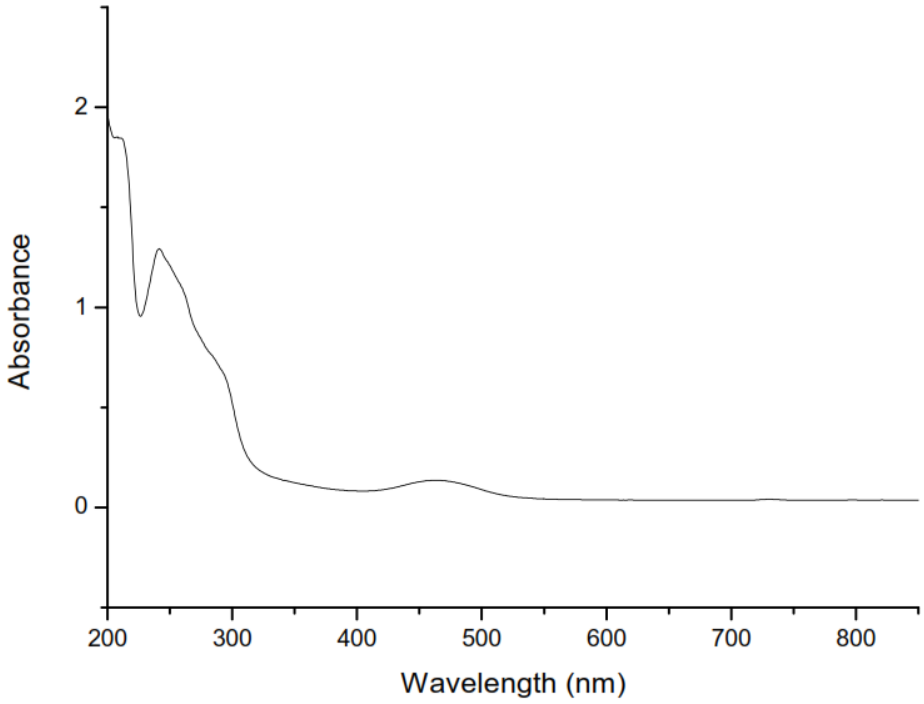


Fig. 4.12 Electronic absorption spectrum of copper complex of L^2

Table 4.8 UV-vis. spectral data of copper complexes

Compound	λ(ν) n- π* transitions	λ(ν) π- π*transitions	λ(ν) d-d transitions
$CuCl_2L^1{}_2$	223 nm (44843 cm^{-1})	293 nm (34126 cm^{-1})	458 nm (21834 cm^{-1})
$CuCl_2\ L^2{}_2.2\ H_2O$		243 nm (41152 cm^{-1})	466 nm (21459 cm^{-1})

4.5.2.2 Electronic absorption spectra of nickel complexes

The electronic spectra of the complexes were recorded in the range of 200-900 nm in acetonitrile solution (10^{-5} M). UV-vis. spectra of the nickel complexes of L^1 displayed bands at (**Fig. 4.13**) at 223 and 290 nm which are assigned to n-π* and π-π* transitions respectively and nickel complex of L^2 displayed bands at (**Fig. 4.14**) 242 and 292 nm which are assigned to n-π* and π-π* respectively (**Table 4.9**).

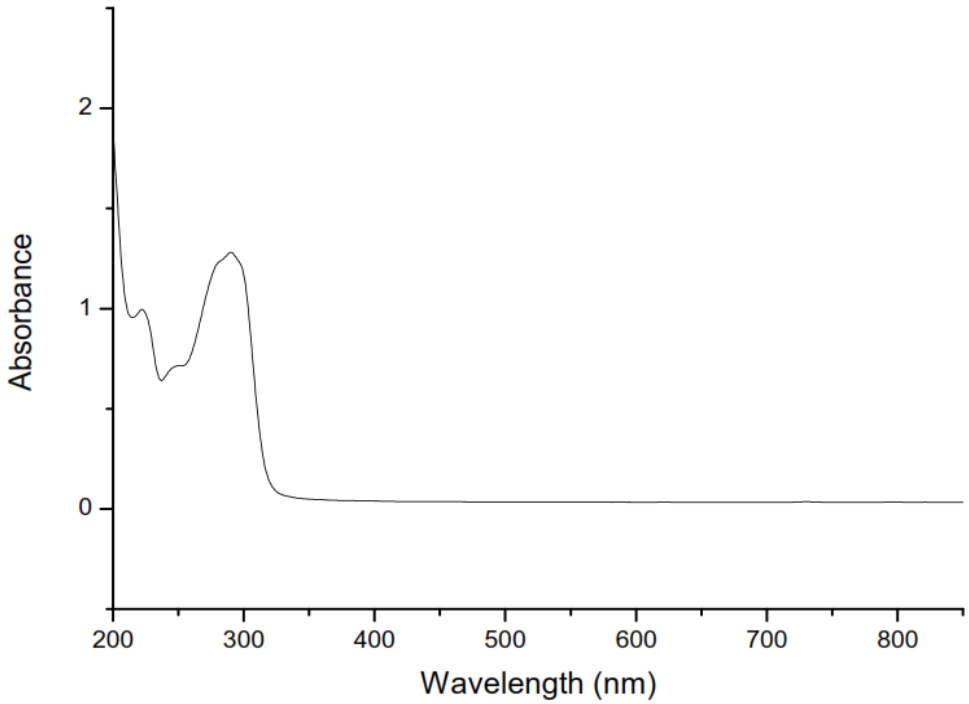


Fig. 4.13 Electronic absorption spectrum of nickel complex of L^1

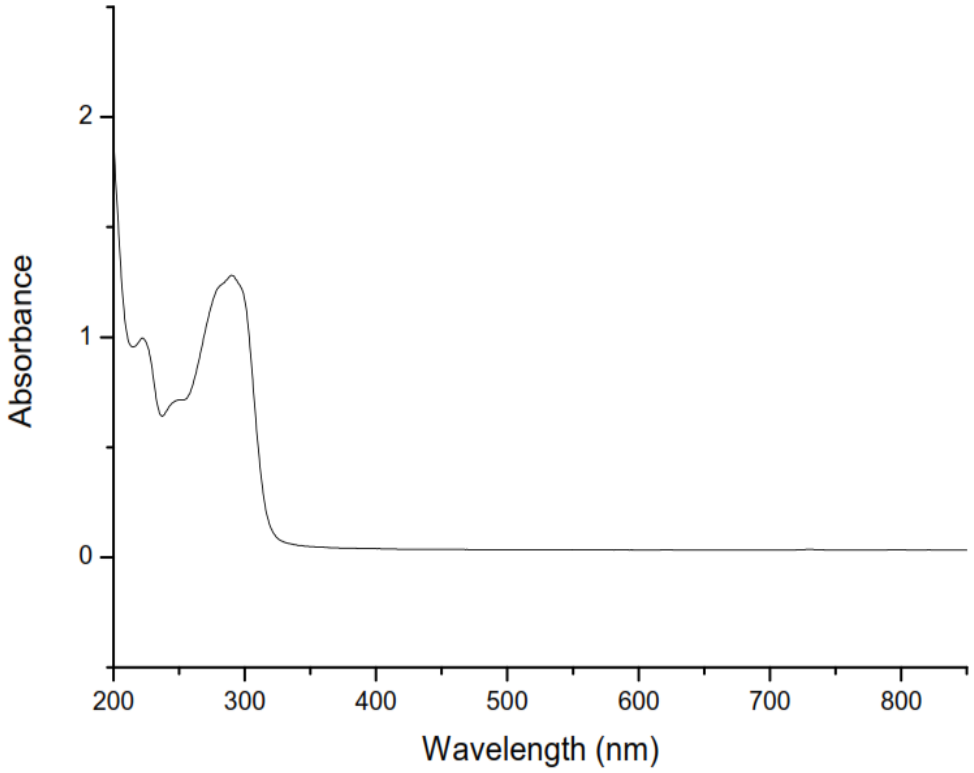


Fig. 4.14 Electronic absorption spectrum of nickel complex of L^2

Table 4.9 UV-vis. spectral data of nickel complexes

Compound	**λ(ν) n- π* transitions**	**λ(ν) π- π*transitions**
$NiCl_2$ L^1_2.2 H_2O	223 nm (44843 cm^{-1})	290 nm (34482 cm^{-1})
$NiCl_2$ L^2_2	242 nm (41322 cm^{-1})	292 nm (34246 cm^{-1})

4.6 EPR spectral studies of copper complexes

EPR spectrum of copper complexes of L^1 was recorded in RT (300 K) as well as LNT (77 K) on X-band at 9.1 GHz frequency and the magnetic field of 3400 G in DMSO as solvent using DPPH as internal reference. In the complex copper ion has oxidation state II and hence

has d^1 electronic configuration. The spectrum at RT shows one intense band at high field region. The EPR spectrum of the powder at RT gave a g_{iso}= 2.10 (A_{iso}= 320). The values of a g_{iso} and A_{iso} are measured using the relation

$$g_{iso} = 1/3(A_{\parallel} + 2\ A_{\perp})$$

$$A_{iso} = (g_{\parallel} + 2\ g_{\perp})$$

At LNT the $g_{\parallel}$ and $g_{\perp}$ (avg) are found to be 2.25 and 2.07 ($A_{\perp}$=315) respectively. $g_{\parallel} > g_{\perp} > 2.0023$ indicate that the unpaired electron is in $d_{x^2-y^2}$ of the Cu(II) ion. In tetragonally distorted octahedral Cu^{2+} complexes having the $d_{x^2-y^2}$ ground state, the hyperfine splitting $A_{\parallel}$ increases when $g_{\perp}$ decreases [122]. It is a characteristic of the axial symmetry with possibly a square planar geometry or a distorted octahedral.

4.7 Antimicrobial studies

The antibacterial activity of ligand, L^2 and its complexes with Ni(II) and Cu(II) were tested against the one Gram positive bacteria, Bacillus subtilis and against one Gram negative bacteria Escherichia coli. The antifungal activity of the ligands and its complexes with Ni(II) and Cu(II) were tested against fungus, Candida albicans. The standard used for antibacterial study is ampicillin and that for antifungal studies is flucanazole. DMSO was used as solvent control. The values of zone inhibition were measured in millimetre. The zone of inhibition against standards and test samples are summarized in **Table 4.10.** The data reveal that the complexes have higher antimicrobial activities than the free ligand and it may be attributed to its higher stability constant [65]. Among the test complexes copper complexes exhibited greater microbial inhibition than the nickel complexes.

Table 4.10 Inhibitory activity of compounds and test organisms

Test compound	**Concentration (µg/25 µL)**	***Escherichia coli***	***Bacillus subtilis***
L^2	25	9.50 ± 0.50	10.50 ± 0.00
$CuCl_2L^2_2.2H_2O$	25	15.50 ± 0.00	14.50 ± 0.00
$NiCl_2L^2_2.2H_2O$	25	11.50 ± 0.00	13.50 ± 0.00
Standard Ampicillin	25	30.00 ± 0.00	35.00 ± 0.00
		Candida albicans	
L^2	25	2.00 ± 0.00	
$CuCl_2L^2_2.2H_2O$	25	4.00 ± 0.00	
$NiCl_2L^2_2.2H_2O$	25	3.00 ± 0.50	
Standard Flucanoazole	25	7.50 ± 0.00	

Chapter 5

Summary and Conclusions

The present work is focused on the synthesis of two novel ligands, Furan-2-carboxylic acid pyridin-4-ylmethyleneamide (L^1) and Thiophene-2-carboxylic acid 1H-indol-2-ylmethyleneamide (L^2). They were characterized by CHNS, FT-IR, ^1H NMR and UV-vis. spectroscopy. Copper and nickel complexes of these ligands were synthesized and characterized by CHNS, FT-IR, EPR, UV-vis. spectroscopy and molar conductance. The ligands and complexes were tested for their antimicrobial activity.

Molar conductivity measurements of the Cu(II) and Ni(II) complexes revealed their non-electrolytic nature in acetonitrile and DMF. FT-IR data showed the presence of lattice water for the copper complex of L^2 and for nickel complex of L^1. Lattice water is absent for copper complex of L^1 and nickel complex of L^2. FT-IR data confirmed the coordination of ligand to the metal ion. ^1H NMR studies of the ligands correspond to the proposed structure. The complexes were not used for the ^1H NMR studies. UV-vis. spectra of complexes were studied for their n-π^* and π-π^* transitions. EPR spectroscopy for the copper complex suggests a distorted octahedral geometry.

The antimicrobial study of the ligand L^2 and its Cu(II) and Ni(II) complexes showed microbial inhibition against the selected test microorganisms of bacteria and fungi. Among the test compounds copper complexes showed higher antimicrobial activity compared to the nickel complexes.

There is further scope of extending this work for biological activity of these complexes. Complexes of other transition metals with these synthesized ligands may also have considerable antimicrobial activity.

References

[1] R. Gare, M. K. Saini, N. Fahmi and V. Singh, "Study of some biorelevant complexes of manganese(II) with active imines," *Indian J. Chem.* , vol.44A, pp.2433-2438, 2005.

[2] R. S. Joseyphus, and M. S. Nair, "Synthesis, characterization and biological studies of some Co(II), Ni(II) and Cu(II) complexes derived from indole-3-carboxaldehyde and glycylglycine as Schiff base ligand," *Arabian J. Chem.* , vol.3, pp.195–204, 2010.

[3] A. Mohd and S. Kumar, "Synthesis of some hydrazone derivatives and their Antinflammatory Activity," *Indian Drugs.*, vol.42, pp.73-77, 2005.

[4] D. Sriram, P. Yogeeswari and K. Madhu, "Synthesis and in vitro and in vivo antimycobacterial activity of isonicotinoyl hydrazones," *Bioorg. Med. Chem. Lett.*

[5] S. Gemma and Kukreja, "N. Synthesis of N1-arylidene-N2quinolyl-and N2-acrydinyl hydrazones as potent antimalarial agents active against CQ resistant P. falciparum strains," *Bioorg. Med. Chem. Lett. Letters*, vol.16, pp.5384-5388, 2006.

[6] B. Narayana Swamy, Synthesis of isonicotinoyl hydrazones from anacardic acid and their in vitro activity against Mycobacterium smegmatis," *Eur. J. Med. Chem.,* vol.42, pp.420-424, 2007.

[7] J. Parekh, P. Inamdhar, R. Nair, S. Baluja and S. Chanda, "Synthesis and antibacterial activity of some Schiff bases derived from 4-aminobenzoic acid," *J. Serb. Chem. Soc.*, vol.70, pp.1155–1161, 2005.

[8] K. S. Kumar, S. Ganguly, R. Veerasamy, and E. De Clercq, "Synthesis, antiviral activity and cytotoxicity evaluation of Schiff bases of some 2-phenyl quinazoline-4(3)H-ones," *Eur. J. Med. Chem.,* vol.45, pp.5474–5479, 2010.

[9] T. O. Aiyelabola, I. A. Ojo, A. C. Adebajo and G. O. Ogunlusi, "Synthesis, characterization and antimicrobial activities of some metal(II) amino acids' complexes," *Adv. Bio. Chem.,* vol.2, pp.268-273, 2012.

[10] H. Yildirim, E. Guler, M. Yavuz and N. Ozturk, "Ruthenium (II) complexes of thiosemicarbazone: Synthesis, biosensor applications and evaluation as antimicrobial agents," *Mat. Sci. Eng.*, vol.44, pp.1–8, 2014.

[11] D.T.Sakhare, "Applications of Metal – Schiff's base Complexes: A Review," *Int. J. Curr. Res. Chem. Pharma. Sci.*, vol.2, pp.22-27, 2015.

[12] P. Govender, N. C. Antonels, J. Mattsson, A. K. Renfrew. J. R. Moss, B. Therrien and G. S. Smith, "Anticancer activity of multinuclear arene ruthenium complexes coordinated to dendritic polypyridyl scaffolds," *J. Org-Met. Chem.*, vol.694, pp.3470-3476, 2009.

[13] H. Li, H. He, Y. Han, X. Gu, L. He, Q. R. Qi, Y. Zhao and L. Yang, "A General Synthetic Procedure for 2-chloromethyl-4(3*H*) quinazolinone Derivatives and Their Utilization in the Preparation of Novel Anticancer Agents with 4-Anilinoquinazoline Scaffolds," *Molecules*, vol.15, pp.9473-9485, 2010.

[14] K. Siddappa and P. C. Reddy, "Synthesis, spectral and antimicrobial studies of some transition Metal(II) complexes with Schiff base 3-[(2-hydroxy-6-methoxyquinolin-3ylmethylene)-amino]-2-methyl-3h-quinazoline-4-one," *Int. J. Appl. Bio. Pharma. Tech.*, vol.3, pp.18-177, 2012.

[15] S. M. Meier, M. Novak, C. A. Davey, M. Hanif, E. Jirkovsky, B. K. Keppler, Z. Adhireksan, M. A. Jakupec, V. Pichler, V. B. Arion and C. G. Hartinger, "Novel metal(II) arene 2-pyridinecarbothioamides: a rationale to orally active organometallic anticancer agents," *Chem. Sci.* , vol.4, pp.1 837-1846, 2013.

[16] N. S. Gwaram and P. Hassandarvish, "Synthesis, characterization and anticancer studies of some morpholine derived Schiff bases and their metal complexes," *J. Appl. Pharma. Sci.*, vol.4, pp.075-080, 2014.

[17] M. M. E. Shakdofa and T. M. A. Abdel-rassel, "Metal complexes of hydrazones and their biological, analytical and catalytic applications: A review," *Main Group Chemistry*, vol.13, pp.187–218, 2014.

[18] H. Sakurai, Y. Fujisawa, S. Fujimoto, H.Yasui, and T. Takino, "Role of Vanadium in Treating Diabetes," *J. Trace Elem. Exp. Med.*, vol.12, pp.393–401, 1999.

[19] H. Sakurai, Y. Fujisawa, S. Fujimoto, H.Yasui, and T. Takino, "Antidiabetic vanadium(IV) and zinc(II) complexes," *Coord. Chem. Rev.*, vol.226, pp.187–198, 2002.

[20] Y. H. Xing, K. A.and F. Y. Bai, "A New Insulin-Like Vanadyl Complex: Synthesis and Structure of V(IV)(H_2O) (2,6-PyridineDicarboxylate)E2H," *Journal of J. Coord. Chem.*, vol.57, pp.157-165, 2004.

[21] M. Hiromur and H. Sakurai, "Action mechanism of metallo-allixin complexes as antidiabetic agents," *Pure Appl. Chem.*, vol.80, pp.2727–2733, 2008.

[22] G. R. Willsky, L. Chi, M. Godzala, P. J. Kostyniak, A. M. Trujillo, J. A. Alfano, W. Ding, Z. Hu, J. J. Smee, D. C. Crans., "Anti-diabetic effects of a series of vanadium dipicolinate complexes in rats with streptozotocin- induced diabetes," *Coord. Chem. Rev.*, vol.255, pp.2258–2269, 2011.

[23] J. Devi and N. Batra, "Oxovanadium(V) complexes with hydrazone ligands: Synthesis, characterization and biological activity," *Der Pharma Chemica*, vol.5, pp.167-173, 2013.

[24] S. Kumar, D. N. Dhar and P. N. Saxena, "Applications of metal complexes of Schiff bases- A review," *J. Sci. Ind. Res.*, vol.68, pp.181-187, 2009.

[25] D. P. Singh, V. Grover, K. Kumar and K. Jain, "Template synthesis and characterization of biologically active transition metal complexes comprising 14-membered tetraazamacrocyclic ligand," *J. Serb. Chem. Soc.*, vol.75, pp.217–228, 2010.

[26] D. P. Singh, V. Grover, K. Kumar and K. Jain, "Synthesis and characterization of divalent metal complexes of the macrocyclic ligand derived from isatin and 1,2-diaminobenzene," *J. Serb. Chem. Soc.*, vol.76, pp.385–393, 2011.

[27] R. N. Patel, "Synthesis of new heterocyclic schiff base, thiazolidinone and azetidinone compounds and their antibacterial activity and anti-hiv activities," *Heterocyclic Lett.*, vol.2, pp.99–105, 2012.

[28] Y. S. Patel, K. D. Patel and H. S. Patel, "Spectral and antimicrobial studies on novel ligand and its co-ordination polymers," *J. Saudi Chem. Soc.*, 2012.

[29] A. P. Mishra, N. Sharma, and R. K. Jain, "Microwave synthesis, spectral, thermal and antimicrobial studies of some Ni(II) and Cu(II) Schiff base complexes," *Avances en Química*, vol.7, pp.77-85, 2012.

[30] G. B. Bagihalli, P. G. Avaji, S. A. Patil, and P. S. Badami, "Synthesis, spectral characterization, in vitro antibacterial, antifungal and cytotoxic activities of Co(II), Ni(II) and Cu(II) complexes with 1,2,4-triazole Schiff bases," *Eur. J. Med. Chem.*, vol.43, pp.2639-2649, 2008.

[31] P. Gull and A. A. Hashmi, "Biological Activity Studies on Metal Complexes of Macrocyclic Schiff Base Ligand: Synthesis and Spectroscopic Characterization," *J. Braz. Chem. Soc.*, vol.26, pp.1331-1337, 2015.

[32] D. P. Singh, V. Grover, K. Kumar and K. Jain, "Synthesis and characterization of divalent metal complexes of the macrocyclic ligand derived from isatin and 1,2-diaminobenzene," *J. Serb. Chem. Soc.*, vol.76, pp.385–393, 2011.

[33] M. Alias, H. Kassum and C. Shakir, "Synthesis, physical characterization and biological evaluation of Schiff base M(II) complexes," *J. Assoc. Arab. Uni. Basic Appl. Sci.*, vol.15, pp.28–34, 2014.

[34] S. Chandra and P. Pipil, "Synthesis, Spectral Characterization and Biological Evaluation of Chromium(III) Complexes of Schiff Base," *Open J. Inorg. Chem.*, vol.4, pp.30-40, 2014.

[35] A. Iqbal, H. L. Siddiqui, C. M. Ashraf, M. Ahmad and G. W. Weaver, "Synthesis, Characterization and Antibacterial Activity of Azomethine Derivatives Derived from 2-Formylphenoxyacetic Acid," *Molecules*, vol.12, pp.245-254, 2007.

[36] D. Kumar, S. Chadda, J. Sharma and P. Surain, "Syntheses, Spectral Characterization, and Antimicrobial Studies on the Coordination Compounds of Metal Ions with Schiff Base Containing Both Aliphatic and Aromatic Hydrazide Moieties," *Bio. Chem. Appl.*, vol.2013, pp.1-10, 2013.

[37] K. Dhaveethu, T. Ramachandramoorthy and K. Thirunavukkarasu, "Microwave-assisted Synthesis of Mixed Ligand Complexes of Zn(II), Cd(II) and Hg(II) Derived from 4-aminopyridine and Nitrite Ion: Spectral, Thermal and Biological Investigations," *J. Korean Chem. Soc.*, vol.57, pp.341-351, 2013.

[38] R. Katwal, H. Kaur and B. Kishore, "Applications of Copper – Schiff's Base Complexes: A Review," *Sci. Revs. Chem. Commun.*, vol.3, pp.1-15, 2013.

[39] A. Prakash and D. Adhikari, "Application of Schiff bases and their metal complexes-A Review," *Int. J. Chem. Tech. Res.*, vol.3, pp.1891-1896, 2011.

[40] M. Shakir and A. Abbasi, "Synthesis and spectral characterization of hydrazone Schiff base ligand, L derived from condensation of terephthalaldehyde and 2-furoic acid hydrazide and its binuclear complexes with Co(II), Ni(II), Cu(II) and Zn(II): Comparative in-vitro microbiological evaluation of L and its Zn(II) coordination complex," *Chem. Pharma. Res.* , vol.7, pp.375-382, 2015.

[41] B. K. Rai and R. Kumari, "Synthesis, Structural, Spectroscopic and Antibacterial Studies of Schiff Base Ligands and their Metal Complexes Containing Nitrogen and Sulphur Donor Atom," *Orient. J. Chem.*, vol.29, pp.1163-1167, 2013.

[42] K. Siddappa and N. S. Mayana, "Synthesis, Spectroscopic Characterization, and Biological Evaluation Studies of 5-Bromo-3-(((hydroxy-2-methylquinolin-7-yl)methylene) hydrazono) indolin-2-one and Its Metal (II) Complexes," *Bio. Chem. Appl.*, vol.2014, 2014.

[43] S. A. Kumbalpuri, A. A. Kachare, S. G. Shankarwar and T. K. Chondhekar, "Synthesis, characterization and antimicrobial activities of Schiff base ligand and its metal complexes," *Der Pharma Chemica*, vol.7, pp.88-93, 2015.

[44] C. Anitha, S. Sumathi, P. Tharmaraj, and C. D. Sheela, "Synthesis, Characterization, and Biological Activity of Some Transition Metal Complexes Derived from Novel Hydrazone Azo Schiff Base Ligand," *Int. J. Inorg. Chem.*, vol.2011, pp.1-8, 2011.

[45] P. V. Rao, K. Ashwini and S. Ammani, "Synthesis and Characterization of Transition Metal Complexes Derived from Some Biologically Active Furoic Acid Hydrazones," *Bull. Chem. Soc. Ethiop.*, vol.21, pp.63-73, 2007.

[46] S. Kumar, S. K. Singh, V. Vardhan and T.R. Sharma, "Characterization of Transition Metal Complexes Derived from Biologically Active Furoic Acid Hydrazone," *Orient. J. Chem.*, vol.28, pp.1837-1840, 2012.

[47] N. S. Reddy, B. S. Shankara, P. M. Krishana and C. Basavaraj, "Synthesis, Characterization, and Antibacterial Activity of Co(II), Ni(II), Cu(II), Zn(II), Cd(II), and Hg(II) Complexes of Schiff's Base Type Ligands Containing Benzofuran Moiety," *Int. J. Inorg. Chem.*, vol.2013, pp.1-10, 2013.

[48] R. S. Yamgar, R. G. Atram, Y. Nivid, S. Nalawade,and S. S. Sawant, Novel Zinc(II) Complexes of Heterocyclic Ligands as Antimicrobial Agents: Synthesis, Characterization, and Antimicrobial Studies," *Bio. Chem. Appl.*, vol.2014, 2014.

[49] Wail Al Zoubi, "Biological Activities of Schiff Bases and Their Complexes: A Review of Recent Works," *Int. J. Org. Chem.*, vol.3, pp.73-95, 2013.

[50] R. Nair, A. Shah, S. Baluja and S. Chanda, "Synthesis and antibacterial activity of some Schiff base complexes," *J. Serb. Chem. Soc.*, vol.71, pp.733–744, 2006.

[51] F. N. Ejiah, T. M. Fasina, O. B. Familoni and F. T. Ogunsola,"Substituent effect on spectral and antimicrobial activity of Schiff bases derived from aminobenzoic acids," *Adv. Bio. Chem.*, vol.3, pp.475-479, 2013.

[52] M. Tumer, D. Ekinci, F.Tumer and A. Bulut, "Synthesis, characterization and properties of some divalent metal(II) complexes: Their electrochemical, catalytic, thermal and antimicrobial activity studies," *Spectrochim. Acta Part*, vol.67, pp.916–929, 2007.

[53] L. E. Chang, C. Simmers and D. A. Knight, "Cobalt Complexes as Antiviral and Antibacterial Agents," *Pharmaceuticals*, vol.3, pp.1711-1728, 2010.

[54] S. Rehman, M. Ikram, S. Rehman, A. Faiz and Shahnawaz, "Synthesis, Characterization and Antimicrobial Studies of Transition Metal complexes of Imidazole Derivative," *Bull. Chem. Soc. Ethiop.*, vol.24, pp.201-207, 2010.

[55] P. Gull and A. A. Hashmi, "Synthesis, characterization and antimicrobial activity of transition metal complexes with Schiff base derived from 1, 2-diphenylethane-1, 2-dione with o-phenylenediamine and benzophenone," *Eur. Aca. Res.*, vol.2, pp.5064-5082, 2014.

[56] P. L. Páez, I. Albesa, C. M. Bazán, M. C. Becerra, M. E. Bongiovanni, and G. A. Argüello, "Oxidative Stress and Antimicrobial Activity of Chromium(III) and Ruthenium(II) Complexes on Staphylococcus aureus and Escherichia coli," *Bio Med Res. Int.*, vol.2013, pp.1-7, 2013.

[57] N. S. Chundawat and M. Pandya, "Antibacterial and antifungal activity of synthesized Schiff's bases and their binary complexes with copper (II)," *World J. Phar. Pharmaceu. Sci.*, vol.4, pp.657-664, 2014.

[58] H. O. Al-Obaidi, "Synthesis, Characterization and Antimicrobial Screening Mixed-Ligand Cu(II) and Zn(II) Complexes: DNA Binding Studies on Cu(II) Complex," *Open J. Inorg. Non-metallic Mat.*, vol.2, pp.59-64, 2012.

[59] H. O. Al-Obaidi, "Synthesis, Characterization and Antimicrobial Screening Mixed-Ligand Cu(II) and Zn(II) Complexes: DNA Binding Studies on Cu(II) Complex," *Open J. Inorg. Non-metallic Mat.*, vol.2, pp.59-64, 2012.

[60] H. Li, H. He, Y. Han, X. Gu, L. He, Q. R. Qi, Y. Zhao and L. Yang, "A General Synthetic Procedure for 2-chloromethyl-4(3*H*)quinazolinone Derivatives and Their Utilization in the Preparation of Novel Anticancer Agents with 4-Anilinoquinazoline Scaffolds," *Molecules*, vol.15, pp.9473-9485, 2010.

[61] M. Hanif and H. Z. Chohan, "Design, spectral characterization and biological studies of transition metal(II) complexes with triazole Schiff bases," *Spectrochim. Acta Part A: Mol. Bio. Spectro.*, vol.104, pp.468–476, 2013.

[62] A. P. Mishra, A. Tiwari, R. Jain, "Microwave Synthesis, Spectral, Thermal and Antimicrobial Studies of Some Ni(II) and Cu(II) Schiff Base Complexes," *Open J. Synth. Theory Appl.*, vol.2, pp.56-62, 2013.

[63] L. Zhang, J. Zhang, X. Zou, Y. Liu, N. Li, Z. Zhang and Y. Li, "Studies on antimicrobial effects of four ligands and their transition metal complexes with 8-mercaptoquinoline and pyridine terminal groups," *Bioinorg. Med. Chem. Lett.*, vol.25, pp.1778–1781, 2015.

[64] P. Ekmekcioglu, N. Karabocek, S. Karabocek and M. Emirik, "Synthesis, structural and biochemical activity studies of a new hexadentate Schiff base ligand and its Cu(II), Ni(II), and Co(II) complexes," *J. Mol. Struct.*, vol.1099, pp.189-196, 2015.

[65] W. H. Mahmoud, N. F. Mahmoud, G. G. Mohamed, Z. El-Sonbati and A. A. El-Bindary, "Synthesis, spectroscopic, thermogravimetric and antimicrobial studies of mixed ligands complexes," *J. Mol. Struct.*, vol.1095, pp.15–25, 2015.

[66] F. Islam, Md. A. Hossain, Md. A. Kabir and N. M. Shah, Mohammad Jamshed Khan, Hridika Talukder Barua, and Romel Mullick, "Synthesis, Characterization, and Antimicrobial Activity Studies of Ni(II) Complex with Pyridine as a Ligand," *J. Chem.*, vol.2015, pp.1-8, 2015.

[67] J. R. Pioquinto-Mendoza, J. A. Rosas-Ortiz, R. Reyes-Martínez, P. Conelly-Espinosa, R. A. Toscano, J. M. Germán-Acacio, A. Avila-Sorrosa, O. Baldovino-Pantaleón and D. Morales, "Synthesis, characterization and molecular structures of Ni(II) complexes derived from Schiff base pyridylimine ligands," *Inorg. Chimica Acta*, vol.438, pp.146–152, 2015.

[68] M. Shakir, A. Abbasi, M. Faraz and A. Sherwani, "Synthesis, characterization and cytotoxicity of rare earth metal ion complexes of N,N'-bis-(2-thiophenecarboxaldimine)-3,3' diaminobenzidene, Schiff base ligand," *J. Mol. Stru.*, vol.1102, pp.108-116, 2015.

[69] H. Zafar, A. Ahmad, A. U. Khan and T. A. Khan, "Synthesis, characterization and antimicrobial studies of Schiff base Complexes," *J. Mol. Stru.*, vol.1097, pp.129–135, 2015.

[70] M. Zaltariov, M. Cazacu, M. Avadanei, S. Shova, N. Vornicu, A. Vlad, A. Dobrov and C. Varganic, "Synthesis, characterization and antimicrobial activity of new Cu(II) and Zn(II) complexes with Schiff bases derived from trimethylsilyl-propyl-p-aminobenzoate," *Polyhedron*, vol.100, pp.121–131, 2015.

[71] K. R. Joshi, A. J. Rojivadiya, and J. H. Pandya, "Synthesis and Spectroscopic and Antimicrobial Studies of Schiff Base Metal Complexes Derived from 2-Hydroxy-3-methoxy-5-nitrobenzaldehyde," *Int. J. Inorg. Chem.*, vol.2014, 2014.

[72] M. Shebl, M. A. El-ghamry, S. M. E. Khalil and M. A. A. Kishk, "Mono- and binuclear copper(II) complexes of new hydrazone ligands derived from 4,6-diacetylresorcinol: Synthesis, spectral studies and antimicrobial activity," *Spectrochim. Acta Part A: Mol. Biomol. Spectro.*, vol.126, pp.232–241, 2014.

[73] H. Ibrahim A. and W. A. Suayed, "Microwave assisted synthesis, characterization, and antimicrobial studies of transition metal complexes of Schiff base ligand derived from isoniazid with 2- hydroxynaphthaldehyde," *Chem. Pharma. Res.*, vol.6, pp.595-602, 2014.

[74] M. Alias, H. Kassum and C. Shakir, "Synthesis, physical characterization and biological evaluation of Schiff base M(II) complexes," *J. Assoc. Arab. Uni. Basic Appl. Sci.*, vol.15, pp.28–34, 2014

[75] R. Bhaskar, N. Salunkhe, A. Yaul and A. Aswar, "Bivalent transition metal complexes of ONO donor hydrazone ligand: Synthesis, structural characterization and antimicrobial activity," *Spectrochim. Acta Part A*, vol.151, pp.621–627, 2015.

[76] B. K. Rai and R. Kumari, "Synthesis, Structural, Spectroscopic and Antibacterial Studies of Schiff Base Ligands and their Metal Complexes Containing Nitrogen and Sulphur Donor Atom," *Orient. J. Chem.*, vol.29, pp.1163-1167, 2013.

[77] S. Kondaiah, G. N. R. Reddy, D. Rajesh and J. Joseph, "Synthesis, Characterization, and Antibacterial Activity of the Schiff Base Derived from P-Toluic Hydrazide and o-Vanilin (OVPTH Ligand) and its Mn(II), Co (II), Ni (II) and Cu (II) Complexes," *Indian Journal of Advances in Chem. Sci.*, vol.1, pp.228-235, 2013.

[78] S. Chandra, M. Tyagi and S. Agrawal, "Spectroscopic and Biological Studies on Newly Synthesized Copper (II) and Nickel (II) Complexes with P-Dimethylaminobanzaldehyde Semicarbazone and P-Dimethylaminobanzaldehyde Thiosemicarbazone," *Int. J. Appl. Bio. Pharma. Tech.*, vol.3, pp.149-159, 2012.

[79] H. N. Al-Shaalan, "Synthesis, Characterization and Biological Activities of Cu(II), Co(II), Mn(II), Fe(II), and UO_2 (VI) Complexes with a New Schiff Base Hydrazone: *O*-Hydroxyacetophenone-7-chloro-4quinoline Hydrazone," *Molecules*, vol.16, pp.8629-8645, 2011

[80] A. S. F. Fabiyi, "Synthesis, Characterization and Antimicrobial Studies of Ruthenium(II) Carboxylates with 3-Hydroxypyridine," *Int. J. Chem.*, vol.3, pp.1-11, 2011.

[81] G. Ceyhan, C. Celik, S. Urus, I. Demirtas, M. Elmastas and M. Tümer, "Antioxidant, electrochemical, thermal, antimicrobial and alkane oxidation properties of tridentate Schiff base ligands and their metal complexes," *Spectrochim. Acta Part A*, vol.81, pp.184– 198, 2011.

[82] Z. You and H. Zh, "Syntheses, Crystal Structures, and Antibacterial Activities of Four Schiff Base Complexes of Copper and Zinc," *Z. Anorg. Allg. Chem.*, vol.630, pp.2754-2760, 2004.

[83] I. Babahan, S. Emirdag-Öztürk and E. Poyrazoglu-Çoban, "Spectroscopic and biological studies of new mononuclear metal complexes of a bidentate NN and NO hydrazone-oxime ligand derived from egonol," *Spectrochim. Acta Part A*, 2015.

[84] M. N. Uddin, D. A. Chowdhury, Md. M. Rony and Md. E. Halim, "Metal complexes of Schiff bases derived from 2-thiophenecarboxaldehyde and mono/diamine as the antibacterial agents," *Mod. Chem.*, vol.2, pp.6-14, 2014.

[85] M. S. Saadeh, "Synthesis, characterization and biological properties of Co(II), Ni(II), Cu(II) and Zn(II) complexes with an SNO functionalized ligand," *Arabian J. Chem.*, vol.6, pp.191–196, 2013.

[86] P.C. Shyma, B. Kalluraya, S. K. Peethambar, S. Telkar and T. Arulmoli, "Synthesis, characterization and molecular docking studies of some new 1,3,4-oxadiazolines bearing 6-methylpyridine moiety for antimicrobial property," *Eur. J. Med. Chem.*, vol.68, pp.394-404, 2013.

[87] A.P. Mishra, A. Tiwari and R. Jain, "Synthesis, spectral, thermal and antimicrobial studies of some transition metal complexes containing 2-thiophenecarboxaldehyde moiety," *Int. J. Res. Pharm. Sci.*, vol.3, pp.167-172, 2011.

[88] S. Chandra, M. Tyagi and S. Agrawal, "Spectral and antimicrobial studies on tetraaza macrocyclic complexes of PdII, PtII, Rh and IrIII metal ions," *J. Saudi Chem. Soc.*, vol.15, pp.49-54, 2011.

[89] C. Spinu, M. Pleniceanu, C. Tigae, "Biologically Active Transition Metal Chelates with a 2-Thiophene- carboxaldehyde-Derived Schiff Base: Synthesis, Characterization, and Antibacterial Properties," *Turk. J. Chem.*, vol.32, pp.487 – 493, 2008.

[90] P. Panchal, H. M. Parekh, P. B. Pansuriya and M. N. Patel, "Bactericidal activity of different oxovanadium(IV) complexes with Schiff bases and application of chelation theory, *J. Enzyme Inhib. Med. Chem*., vol.21, pp.203–209, 2006.

[91] R. A. Shiekh, S. Shreaz, L. A. Khan and, A. A. Hashmi, "Development and characterization of bioactive macrocyclic metal complexes, use as a potential drug," *Chem. Pharma. Res.*, vol.2, pp.172-185, 2010.

[92] V. V. Raju, K. P. Balasubramanian, C. Jayabalakrishnan and V. Chinnusamy, "Synthesis, spectral characterization, catalytic and biological studies of new Ru(II) carbonyl Schiff base complexes of active amines," *Natural Sciences,* vol.3, pp.542-550, 2011.

[93] Z. H. Chohan, S. H. Sumrra, M. H. Youssoufi and T. B. Hadda, "Metal based biologically active compounds: Design, synthesis, and antibacterial/ antifungal/ cytotoxic properties of triazole-derived Schiff bases and their oxovanadium(IV) complexes," *Eur. J. Med. Chem.*, vol.45, pp.2739-2747, 2010.

[94] K. Singh, Y. Kumar, P. Puri and G. Singh, "Spectroscopic, Thermal, and Antimicrobial Studies of Co(II), Ni(II), Cu(II), and Zn(II) Complexes Derived from Bidentate Ligands Containing N and S Donor Atoms," *Bio. Chem. Appl.*, vol. 2012, pp.1-9, 2012.

[95] R. Kothari and B. Sharma, "Synthesis, characterization, antibacterial, antifungal, antioxidant and DNA interaction studies of thiosemicarbazone transition metal complexes," *World J. Pharm. Pharmaceu. Sci.*, vol.3, pp.1067-1080, 2014.

[96] S. Nadeem, M. Sirajuddin, S. Ahmad, S. A. Tirmizi, M. I. Ali and A. Hameed, "Synthesis, spectral characterization and in vitro antibacterial evaluation and Petra/Osiris/Molinspiration analyses of new Palladium(II) iodide complexes with thioamides," *Alex. J. Med.*, 2015.

[97] J. N. Asegbeloyin, E. P. Coban, O. T. Ujam, A. Özmen, E. C. Okafor and H. Biyik, "Synthesis, Characterization, and Biological Activity of N'-[(Z)-(3-Methyl-5-oxo-1-phenyl-1,5-dihydro-4H-pyrazol- 4ylidene) (phenyl) methyl] benzohydrazide and Its Co(II), Ni(II), and Cu(II) Complexes," *Bio. Chem. Appl.*, vol.2014, pp.1-11, 2014.

[98] M. Tayebani and M. Iravani, "Spectroscopic studies and biological evaluation of some transition metal complexes of Schiff-base ligands derived from pyridine-2-carbaldehyd," *J. Chem. Pharma. Sci*., vol.5, pp.89-96, 2014.

[99] J. R. Gujarathi, N. S. Pawar and R. S. Bendre, "Synthesis, spectral and biological study of four and five co-ordinate copper (II) complexes derived from 5-chloro-2-hydroxy acetophenone N(4)-methyl thiosemicarbazone," *Der Pharma Chemica*, vol.5, pp.111-117, 2013.

[100] S. Chandra and A. Gupta, "Synthesis, spectroscopic, and antimicrobial studies on bivalent Nickel(II) and Copper(II)complexes with 2,6-diacetyl pyridine bisthiosemicarbazone," *Chem. Pharma. Res.*, vol.5, pp.278-285, 2013.

[101] K. Eshwari, P. Saroja, K. Sandhya, B. Sireesha, P. Raghavaiah, and C. S. Devi, "A Study on Structural Aspects and Microbial Activity of (E)-4-pyridinecarboxaldehyde-3-Hydroxy-5-(Hydroxymethyl)-2-Methyl-Oxime Hydrochloride: An Experimental and Computational Approach," *J. Chem. Pharm. Res*., vol.6, pp.167-173, 2014.

[102] M. Meera, S. A. Padusha, H. El-Hamshary and S.S. Al-deyab, "Synthesis, characterization and antimicrobial study of N-Mannich base and its complex," *Der Chemica Sinica*, vol.4, pp.93-99, 2013.

[103] A. P. Mishra, A. Tiwari. S. K. Gupta and R. Jain, "Synthesis of New VO(II), Co(II), Ni(II) and Cu(II) Complexes with Isatin-3-Chloro-4-Floroaniline and 2-Pyridinecarboxylidene-4- Aminoantipyrine and their Antimicrobial Studies," *Mycobiology*, vol.40, pp.20-26, 2012.

[104] P. Venkateswara Rao, G.S. Prasad and P. S. S. Prasad, "Novel synthesis, characterization and biologicalStudies of Schiff base complexes of 4-pyridine Carboxaldehyde," *Int. J. Pharma. Dev. Tech*., vol.4, pp.245-248, 2014.

[105] A. Kajal, S. Bala, S. Kamboj, N. Sharma, and V. Saini, "Schiff Bases: A Versatile Pharmacophore," *J. Cat.*, vol.2013, pp.1-14, 2013.

[106] K. Hariprasath, B. Deepthi, I. Sudheer Babu, P. Venkatesh, S. Sharfudeen and V. Soumya, "Metal Complexes in Drug Research -A Review," *Chem. Pharma. Res.*, vol.2, pp.496-499, 2010.

[107] R. Katwal, H. Kaur and B. K. Kapur, "Applications of Copper –Schiff's Base Complexes: A Review," *Sci. Revs. Chem. Commun.*, vol.3, pp.1-15, 2013.

[108] Rajni and L. Singh, "A review on synthesis and application of macrocyclic ligands and their transition metal complexes," *Int. J. Adv. Eng. Appl.,* vol.6, pp.74-88, 2013.

[109] M. B. Smith and J. March, "March's Advanced Organic Chemistry Reactions, Mechanisms and Structure*," 6th ed., John Wiley & Sons, Inc., Hoboken*, New Jersey, 2007.

[110] F. A. Carey, "Organic Chemistry," 5th ed., *The McGraw-Hill Companies, Inc.,* New York, 2003**.**

[111] P. A. Vigato and S. Tamburini, "The challenge of cyclic and acyclic Schiff bases and related derivatives," *Coord. Chem. Rev.*, vol.248, pp.1717-2128), 2004.

[112] G. Kumar, "Synthesis, spectral characterization and antimicrobial evaluation of Schiff base Cu (II), Ni (II) and Co (II) complexes," *Eur. J. Med. Chem.,* vol.45, pp.3056-3062, 2010.

[113] J. Chakraborty, "Synthesis, characterisation and crystal structures of three trinuclear cadmium(II) complexes with multidentate Schiff base ligands," *Polyhedron,* vol.26, pp.5139–5149, 2007.

[114] P. Mukherjee, O. Sengupta, M. G. B. Drew, and A. Ghosh, "Anion directed template synthesis of Cu(II) complexes of a N,N,O donor mono-condensed Schiff base ligand: A molecular scaffold forming highly ordered H-bonded rectangular grids," *Inorg. Chimica Acta*, vol.3362, pp.3285-3291, 2009.

[115] M. A. Neelakantan, "Spectral characterization, cyclic voltammetry, morphology, biological activities and DNA cleaving studies of amino acid Schiff base metal(II) complexes", *Spectrochim. Acta part A,* vol.*71, pp.1599, 2008.*

[116] M. Poonkothai and B. S. Vijayavathi, "Short Communication Nickel as an essential element and a toxicant," *Int. J. Env. Sci.*, vol.1, pp.285-288, 2012.

[117] S. W. Ragsdale, "Nickel-based Enzyme Systems," *J. Bio. Chem., vol.*284, pp.18571-18575, 2009.

[118] S. Kumar and A. V. Trivedi, "A Review on Role of Nickel in the Biological System," *Int. J. Curr. Micro.Appl. Sci.*, vol.5, pp.719-727, 2016.

[119] S. Lovely and M. Christudhas, "Synthesis, characterization and biological activities of Schiff base complexes of Cu(II), Ni(II), and Co(II) with 4-pyridine carboxaldehyde and 3-aminopyridine," *Chem. Pharma. Res.*, vol.5(2), pp.184-191, 2013.

[120] A. Tadjarodi and S. Najjari, "Microwave-assisted synthesis of Cd (II) complex of 4-pyridinecarboxaldehyde thiosemicarbazone,"

[121] D. H. Busch, "Structural definition of chemical templates and the prediction of new and unusual materials," *J. Phen. Mol. Rec. Chem*., vol.12, pp 389–395, 1992.

[122] S. K. Hoffmann, J. Goslar, S. Lijewski and A. Zalewska, "EPR and ESE of CuS_4 complex in $Cu(dmit)_2$: g-factor and hyperfine splitting correlation in tetrahedral Cu-sulfur complexes," *J. Mag. Reso.*, vol.236, pp.7-14, 2013.