DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF TRANSITION METAL COMPLEXES BY USING MANNICH BASE LIGANDS

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By

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BONAFIDE CERTIFICATE

This is to certify that the thesis entitled **"DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF TRANSITION METAL COMPLEXES BY USING MANNICH BASE LIGANDS"** submitted by **Mr. K. GOVINDARAJAN** to the **BHARATHIDASAN UNIVERSITY, Tiruchirappalli - 24** for the award of the degree of **Doctor of Philosophy** by Research is a Bonafide Record of research work carried out under my supervision. The contents of this thesis, in full or in parts, have not been submitted to any other Institute or University for the award of any degree, diploma, associateship, fellowship or any other similar title and that it represents entirely an independent work on the part of the candidate.

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DECLARATION

I do hereby declare that the work presented in the thesis entitled **"DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF TRANSITION METAL COMPLEXES BY USING MANNICH BASE LIGANDS"** Submitted by me to the **BHARATHIDASAN UNIVERSITY** Tiruchirappalli-24 for the award of the degree of **Doctor of Philosophy in Chemistry** by Research is an original record of research work carried out by me under the supervision of **Dr. M. Ramesh, Assistant Professor, PG and Research Department of Chemistry, Nehru Memorial College (Autonomous) Puthanampatti, Tiruchirapalli**. The contents of this dissertation, in full or in parts, have not been submitted to any other Institute or University for the award of any degree or diploma, membership, fellowship, associate ship etc. In keeping with the general practice in reporting scientific observation, due acknowledgement has been made whenever the work described is based on the findings of other investigators.

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K. GOVINDARAJAN

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ABBREVIATION

DNA	deoxyribonucleic acid
µg/g	Microgram per gram
SOD	superoxide dismutase
mg	Milligram
pH	Negative log of hydrogen ion concentration
B.M	Magnetic moment
MBU	morpholinobenzylurea
PBU	piperidinobenzylurea
ALB	Al-Li-bisbinaphthoxide
MIC	Minimum inhibitory concentration
CNS	Central Nervous System
mg	Milligram
kg	Kilogram
HIV	human immunodeficiency virus
MDR	multidrug-resistant
MBU	N,N'-bis(N-morpholinobenzyl)
PBU	N-(l-piperidinobenzyl)urea
g	Gram
mL	Millilitre
DMSO	Dimethylsulfoxide
KBr	Potassiumbromide
M	Molar
cm	Centimetre
nm	Nanometre
CMC	2-((2,6-dioxocyclohexyl)(2-hydroxyphenyl)methyl)hydrazine carboxamide
CMU	1-((2,6-dioxocyclohexyl)(2-hydroxyphenyl)methyl)urea
CMT	1-((2,6-dioxocyclohexyl)(2-hydroxyphenyl)methyl)thiourea
1a	$[Cu(CMC)_2Cl_2]$

1b	$[Ni(CMC)_2Cl_2]$
1c	$[Fe(CMC)_2Cl_2]$
1d	$[Cr(CMC)_2Cl_2]$
1e	$[Mn(CMC)_2Cl_2]$
2a	$[Cu(CMU)_2Cl_2]$
2b	$[Ni(CMU)_2Cl_2]$
2c	$[Fe(CMU)_2Cl_2]$
2d	$[Cr(CMU)_2Cl_2]$
2e	$[Mn(CMU)_2Cl_2]$
3a	$[Cu(CMT)_2Cl_2]$
3b	$[Ni(CMT)_2Cl_2]$
3c	$[Fe(CMT)_2Cl_2]$
3d	$[Cr(CMT)_2Cl_2]$
3e	$[Mn(CMT)_2Cl_2]$

ABSTRACT

One of the really fascinating scientific disciplines is inorganic chemistry. Coordination chemistry is one of the many areas investigated in inorganic chemistry. A coordinated or complex molecule has a core metal ion or atom wrapped by ligands, which are donating sites. Lewis acids are metal atoms or ions, while Lewis bases are ligands.

The area of coordination chemistry is seeing an upsurge in current research over the past two decades. This is mainly owing to the fact that inorganic chemists now have access to a variety of good physical methods. Further cause for coordination chemistry's fast growth is the discovery of ligand field, crystal field, and molecular orbital hypotheses, some of which could adequately determine the behaviour of bond formation in complexes and different empirical studies. The 3d-transition elements have drawn a lot of attention because the spectral and magnetic characteristics of the coordination compounds of such metal ions allow one to accurately anticipate the stereochemistry of certain molecules. A search of the literature shows that transition metals have become the topic of much research.

Coordination chemistry, as a field of inorganic chemistry, is progressing at an unparalleled rate, either empirically and conceptually. It has witnessed a significant increase in the number of scientific techniques in recent times, as well as a strong emphasis on theoretical treatment. Inorganic scientists did not think about applying contemporary inorganic chemistry to living organisms until the 1950s. Numerous physical and biological scientists are interested in metallo-macromolecules because of their unusual properties. Inorganic chemistry, particularly bioinorganic chemistry, has

sparked interest as a result of recent interesting discoveries in biochemistry. Bioinorganic chemistry, according to William [13], is the physiology of living systems' coordination molecules. Chlorophyll, hemoglobin, and other coordination molecules of a certain kind are all recognized.

The finding of disease-causing microorganisms prompted humanity to devise a strategy for eliminating microbes in and around the living activity. The quest for compounds with strong antibacterial activity becomes an important field of study in this age as a result of this push. The toxicity of chemical compounds as antimicrobes to both host and microbial cells is a significant drawback. As a result, the chemical compounds employed should be selectively poisonous to dangerous bacteria while being nontoxic to host tissues. As a result, scientists must be continuously creating and evaluating novel chemicals for antibacterial efficacy. Transition metal complexes having numerous pharmacological applications. Keep this in mind, we synthesize transition metal complexes (**1a-1e**), (**2a-2e**), (**3a-3e**) by using pharmacologically active mannich base ligands (**1-3**) and screened for antibacterial and antifungal activity against several bacterial and fungal strains.

INTRODUCTION

CHAPTER - I
INTRODUCTION

1. Inorganic chemistry

One of the really fascinating scientific disciplines is inorganic chemistry. Coordination chemistry is one of the many areas investigated in inorganic chemistry. A coordinated or complex molecule has a core metal ion or atom wrapped by ligands, which are donating sites. Lewis acids are metal atoms or ions, while Lewis bases are ligands.

The area of coordination chemistry is seeing an upsurge in current research over the past two decades. This is mainly owing to the fact that inorganic chemists now have access to a variety of good physical methods. Further cause for coordination chemistry's fast growth is the discovery of ligand field, crystal field, and molecular orbital hypotheses, some of which could adequately determine the behavior of bond formation in complexes and different empirical studies. The 3d-transition elements have drawn a lot of attention because the spectral and magnetic characteristics of the coordination compounds of such metal ions allow one to accurately anticipate the stereochemistry of certain molecules. A search of the literature shows that transition metals have become the topic of much research.

Complexation is a fairly universal phenomena, although it is particularly noticeable amongst transition metals. The metal must have symmetrically accurate, sterically accessible, and low-energy empty d-orbitals in order to bind. Transition metal ions are the finest at meeting these criteria, therefore it's no surprise since can produce complexes easily.

Several different ligands are employed in conjunction with transition metal ions. Heterocyclic compounds with oxygen and nitrogen contributors, for example, are thought to be possible ligand sites for coordination to metal atoms. It is commonly recognised that in multiple outlets, such ligands bind to a metal atom in various manner. Despite the fact that oxygen and nitrogen-containing heterocycles are employed as ligands, a variety of coordination mechanisms alone has received much interest [1-7]. Complexes using nitrogen as the donating element will be more stable if they produce a chelate rings. The complexation of these kind of ligands on copper and nickel to create intriguing series of coordination compounds is documented in the chemical literature. Nickel (ll) macrocyclic molecules with heterocyclic ligands, DNA model with copper (II), and dimeric chelating agents of copper and nickel ions with this ligands were all widely investigated. Numerous researchers have highlighted most of those key characteristics of certain oxygen and nitrogen binding complexes [8-12].

Compounds having an amide backbone, along with urea, thiourea, and semicarbazide, were utilized as ligands with transition metal ions like copper, nickel, cobalt, iron, and zinc in this study. The Mannich reaction is used to make all of the ligands, therefore it's important to understand how it works.

1.1. Coordination chemistry

Photosynthesis, enzymatic metabolism, electron and oxygen transportation, and a variety of many other physiological systems are all explained by coordination chemistry. The fundamentals of coordination compounds have spawned a slew of other disciplines, including bioinorganic chemistry and organometallic chemistry, each with its own set of industrial uses.

Coordination chemistry, as a field of inorganic chemistry, is progressing at an unparalleled rate, either empirically and conceptually. It has witnessed a significant increase in the number of scientific techniques in recent times, as well as a strong emphasis on theoretical treatment. Inorganic scientists did not think about applying contemporary inorganic chemistry to living organisms until the 1950s. Numerous physical and biological scientists are interested in metallo-macromolecules because of their unusual properties. Inorganic chemistry, particularly bioinorganic chemistry, has sparked interest as a result of recent interesting discoveries in biochemistry. Bioinorganic chemistry, according to William [13], is the physiology of living

systems' coordination molecules. Chlorophyll, hemoglobin, and other coordination molecules of a certain kind are all recognized.

Bioinorganic chemistry is a fast expanding branch of research that bridges the gap between inorganic and organic chemistry. Metal ions' significance in living organisms has long been recognized, but rigorous research into their structural and metabolic functions has only just begun. Metal ions like sodium, potassium, calcium, and others are found in relatively significant levels in living creatures, while many others, like iron, copper, zinc, manganese, molybdenum, chromium, and vanadium, are found in low concentrations. Although an adult's entire metal content is just 2% of their body mass, living cannot exist without them. As a result, the importance of metal ions and metal complexes in living organisms has grown.

1.2. The importance of transition metal ions in human biology

There are two types of nutrients which are essential for human metabolic processes: macro elements and trace elements. Our research focuses on such trace components. Metals in biological samples at quantities less than 1µg/g body mass make up the trace elements. They interact with vitamins to create enzymes and are required for nearly all biochemical functions. If any of the minerals are lacking, the body will not operate correctly. Certain trace elements are important nutrients for people and pets, such as cobalt, selenium, molybdenum, iron, zinc, nickel, chromium, manganese, and copper.

Hint rudiments may be originate in a wide variety of animals and plants diets, in addition to certain elements can still be identified in drinkable water. Charges, mobilities, and binding affinities to physiological ligands dictate the roles of trace elements. Those around form relatively stable compounds with enzymes, nucleic acids, as well as other ligands, while others may be employed as charge carriers to transmit electrical signals through nerves, for example. Some create solid static complexes and develop an essential component of proteins and enzymes, whereas others serve as triggers/activators regulating biological processes. Numerous biological processes rely on dietary micronutrients as a result (e.g. copper, zinc, etc.,).

The goal of this research is to synthesize and characterize complexes of Mannich bases including Fe (II), Cu (II), Ni (II), Cr (II) and Mn (II) ions. The biotic significance of these metals, as well as its function in regular organisms, were addressed in the following sections.

1.2.1. Copper

Much has been learned about copper's essential biological functions and copper-dependent enzymes during the last 70 years. Copper is linked to storage proteins (metallothioneins), carrier proteins (copperalbumin and ceruloplasmin), and copper encompassing enzymes in human bodies [14]. The human body has a significant quantity of a metalloenzymes of copper. Cu is required for the

appropriate function of copper-reliant enzymes such as superoxide dismutase (SOD), (antioxidant production), dopamine hydroxylase (catecholamine production), lysyl oxidase (collagen and elastin formation), cytochrome C oxidase (energy production), tyrosinase (pigmentation and protein synthesis), ceruloplasmin and clotting factor V (blood clotting).

The primary enzyme tangled in the required bridging of connective tissue is lysyl oxidase. The correct cross-linking of elastin and collagen, which is essential for the flexibility and strength of human fibrous tissue, is ensured by lysyl oxidase's optimal action.

Copper comes in three different states in complexes: Cu (I), Cu (II), and Cu (III). Cu (III) is often considered as rare due to its ease of reduction, although it has recently gained significance due to its role in biochemical functions [16]. The only Cu (III) combination with a high spin is K_3CuF_6, with the others being low spin diamagnetic [17]. Cu (II) produces complexes through ligands that provide oxygen and nitrogen. Cu (II) can conduct redox reactions utilizing thiols moiety in protein. Nitrogen ligand Cu (II) complexes are typically more stable over Cu (I) complexes [18]. Cu (II) co-ordination numbers 4, 5 and 6 are the most frequent, although normal geometries are uncommon, and distinguishing among square-planar and tetragonally deformed octahedral co-ordination is difficult. Schiff bases [19], which include

mixed O and N donor ligands, are interesting because they show square-planar co-ordination and squarepyramidal co-ordination dimerization.

Copper is the 3rd most frequent and important transition metal on the planet. Copper has an important part in the biological process of life. Copper is antimicrobial in nature. All living creatures need trace amounts of copper to sustain normal cellular functioning [20-22]. Based on the chemical reactivity, a living person having approximately 100mg of copper is highly hazardous. Living organisms have developed systems to save copper when nutritional levels are low and to remove unnecessary copper from the system when it is required. Wilson's illness is caused by a hereditary failure to eliminate copper, resulting in copper buildup. Here between erythrocytes and the plasma, copper is dispersed in different ratios in whole blood. Copper is carried via the bloodstream as ceruloplasmin (95%), albumin (5%), and low-molecular-weight copper complexes [23-24]. Wilson's illness and Menkes kinky hair disease [26] are two fatal inherited diseases [25] caused by copper absorption problems.

Copper intake is regulated by a mechanism that is not well known, as is the method by which copper penetrates biological membranes. Copper may be absorbed from the stomach and the whole small intestine, according to research [27,28]. At the upper illenium or duodenal end of the gastrointestinal system, absorption is quick. Low-molecular-weight compounds are essential in promoting copper

transport through cell membranes in different tissues. Age, hormones, illness, and nutrition all have an impact on tissues copper concentrations. Copper levels in the blood of rheumatoid arthritis sufferers have been found to be unusually high. Copper urine concentrations were shown to be high in patients with rheumatoid arthritis, according to McMurray et al [29]. Our current knowledge of copper absorption, transportation, storing, and eventual use does not clearly describe how metabolic antagonism in the food or environment may disrupt these mechanisms. It's also difficult to predict the effects of hereditary copper metabolic abnormalities accurately.

Copper is found in a variety of foodstuffs. The rich alternatives are dry beans and nuts. Copper is mostly obtained via the dietary and is originate in mineral-rich nutriments for example fruits, vegetables, nuts, grains, chocolate, and legumes. Copper is a naturally occurring metal that may be originate in the globe's layer as well as water surface. Copper is also present in groundwater that is utilized for drinking. Copper may be transmitted from the surface of some meals and beverages stored in copper crockery for a long length of time. The National Research Council has determined that a daily copper consumption of 2-3 milligrams is healthy and sufficient for humans [30]. Supplementing with 3 milligrams of copper every day is recommended for those who eat a lot of vitamin C and zinc.

When compared to conventional manufactured complexes, copper metal in biological processes exhibits some unusual characteristics. The high absorption in the range of 600 nm is the most distinguishing feature of a blue copper site and the foundation of the name "blue copper." Copper has been known to have anti-inflammatory and anti-ulcer properties since Walker, Griffen [31], and Sorenson [32]. Brown et al [33] and others investigated the pharmacological functions of a variety of Cu(II) and Cu(I) complexes using active and inert ligands.

1.2.2. Cobalt

Cobalt is required for the survival of all higher creatures. Cobalt is an essential component of vitamin B12, which is required for proper erythrocyte production in the bone marrow. Meat, milk products, and leafy green vegetables are all good sources of cobalt. Cobalt chelates have antiviral properties. The discovery of vitamin B12, which includes cobalt, resulted in the creation of anti-pernicious anemia in the liver. Several antibiotics, most notably penicillin, have a synergistic action with cobalt compounds [34]. While biological ecosystems seem to utilize iron and copper primarily for activities, research investigation of cobalt complexes as templates for biological processes has yielded a wealth of valuable knowledge [35]. Ocular herpes virus multiplication has been found to be inhibited by cobalt (III) Schiff base complexes.

In porphyrin complexes, the cobalt element is connected to four nitrogen atoms, forming the framework for a highly conjugated tetrapyrrole structure. Alkylation occurs after vitamin B12 interacts to adenosine triphosphate, forming a direct carbon-cobalt link among adenosine and cobalt. This group of enzymes is known as B12 coenzymes. B12 coenzymes are formed via homolytic breakage of the cobalt-carbon link, that produces a 5'-deoxyadenosyl radicals and Co (II) atom a, which may rejoin through the Co (II) atom to create a coenzyme.

1.2.3. Nickel

Nickel is a micronutrient that is required for survival. Oatmeal, legumes, almonds, chocolate, whole wheat bread, and certain green vegetables like kale and lettuce are good sources of nickel. Nickel is consistently present in blood and tissues, and it is also linked with DNA and RNA in physiologically significant quantities. Nickel is needed for proper animal development and reproduction, and it is likely that it is also essential for human growth and reproduction. It seems to have a function in immune system regulation as well as brain function. The activity of spleen B- and T-cells is increased by nickel, while thymocyte action is unchanged. The function of spleen natural killer cells diminishes, while blood cell population increases. With nickel therapy, the amount of Mac 2+ cells, helper T-cells, and cytotoxic T-cells, in cardiac defects reduces. These findings indicate that nickel may have a role in the development of acute renal dysfunction in CBC-induced auto

immunological and/or inflammatory diseases including diabetes and myocardial infarction. Nickel has a serious influence on immune system, causing natural killer cell activity to alter and macrophage recruitment into inflammatory lesions to diminish. In biological chemistry, nickel is a fascinating and adaptable metal [36]. It is a necessary element of many metalloproteins and also helps to decrease DNA damage and protein-DNA cross - linking caused by an ecological carcinogen. Nickel, in the presence of tetraazamacrocyclic complexes, offers a methodology for molecular biologists to investigate nucleic acid architecture. Nickel has now been linked to pigmentation and the activation of a variety of metals associated to ribonucleic acids [37]. Nickel has been found in at least four different kinds of biological entities since 1980, including

1. Plant-derived urease

2. Sulphate-reducing, methanogenic, photosynthetic, nitrogen-fixing, and "knall gas" bacteria have hydrogenases.

3. Acetogenic bacteria having CO dehydrogenases

4. A tetrapyrrole prosthetic group factor F430 with a low molecular weight that is found in methanogenic bacteria.

1.2.4. Zinc

Zinc is among the most essential metals in biology, and it seems to be required for all kinds of life. Zinc is found in approximately 2 grams of an adult person's

body, although its content is extremely low. The liver, prostrate, voluntary muscles, and bones are the major sources of zinc [38]. Zinc prefers to create constant complexes through enzymes and proteins owing to its d^{10} electronic structure [39,40]. It is a necessary component of carboxypeptidase-A and carbonic anhydrase, since CO2 transfer would not be possible without that. Zinc is often thought to help maintain Vitamin A levels in the blood through liberating it from the liver [41]. Burns [42], surgical incisions [43], ulcers [44], diabetes [45], and sickle cell anemia [46] have all been shown to benefit from supplements. Zinc is thought to have a role in insulin production and storage in β-cells. Its absence results in a pre-diabetic state [47]. As antifungal agents, soaps (salts of fatty acids, such as zinc stearate) are employed. Zinc is an antibacterial mineral that is commonly used in skincare.

Zinc may be originate in a diversity of foodstuffs such as whole grains, beans, shellfish, milk products, and nuts. Oysters have the highest zinc content of somewhat foodstuff, although red chicken meat also contribute significantly. Zinc is a component that is present in nearly each cell in the body. It increases the activity of around 100 enzymes [48]. Zinc is required for healing process, the senses of smell and taste, and DNA synthesis, among other things [49-51].

Zinc produces stable compounds through ligands including halides of O,N,S, , and CN^- mixes of Zn (II) ions generally colorless and diamagnetic. There is no crystal field stabilization in the d10 setup. The polarizing strength and size of the Zn

(II) ion, along with the steric demands of the ligands, determine the stereochemistry of a given molecule. As a result, four coordinated tetrahedral complexes are preferred by Zn (II). Zinc has a nearly constant oxidation state of 2+ due to its full d10 valence and two extra s electrons. It does not seem to be oxidized or reduced in biochemical functions. It typically appears planar complexes, although it may also produce octahedral complexes. The ligand size, electrostatics, and kind of bond all have a role in the stereochemistry of Zn (II) complexes. Zn (II) prefers to serve as a metabolic antagonist towards Cu (II) because of comparable electronic structure, charges, and size.

Zinc functions as a coenzyme in a variety of metabolic processes. Zinc is present in several metalloenzymes, including carboxy peptidase and carbonic anhydrase, as a Lewis acid for the reasons listed:

1. There are no ligand field issues connected with Zn (II) that may be used to establish a specific coordination number or geomentry.
2. On Zn (II), ligand exchange activities are so fast both substrates and products may be added and withdrawn quickly.
3. Zn (II) is present in a variety of model systems.
4. At low pH, Zn (II) does not hydrolyze to produce hydroxo complexes.

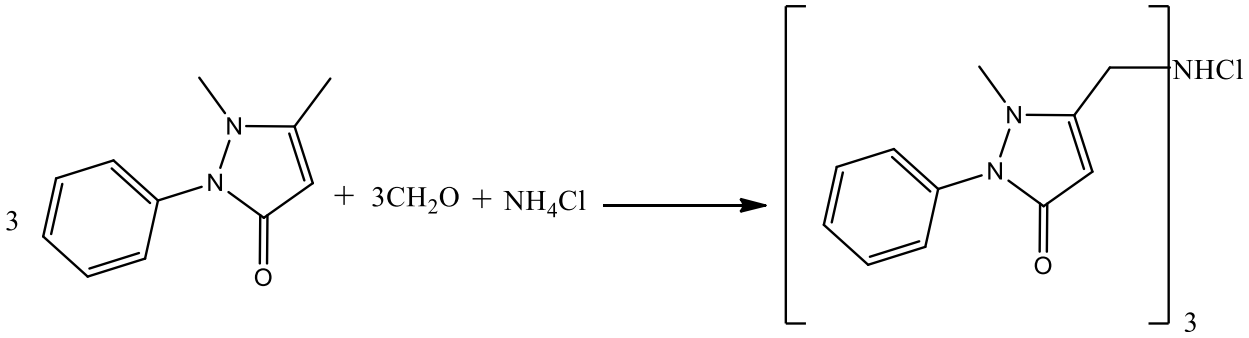
Free ionic zinc in salivary reduces the length and intensity of common cold symptoms, according to a research by Novak et al [52]. Zinc is being used in the

treatment and prevention of the common cold in the lack of an efficient therapy. The blood zinc content fluctuations in people with symptomatic hepatitis B and the early recovery phases were investigated by Fota-Markowska et al [53]. Zinc has a role in HIV viral replication in a variety of ways [54]. Zinc levels in the blood are commonly reduced in HIV patients. Zinc in the extracellular matrix is essential in the fight towards HIV infection.

1.3. The Mannich reaction

1.3.1. Chemistry of Mannich reaction

Tollens [55], who extracted the tertiary amine using formaldehyde, acetophenone, and ammonium chloride, reported the former detection of a condensation of the kind nowadays recognized as Mannich reaction. In 1912, when Carl Mannich [56], a younger researcher in the pharmacological research laboratory at Gottingen University, were preparing a salicylantipyrine acid solution using hexamethylene tetramine (urotropine) for pharmacological manufacture, a serendipitous event occurred. He ended up with a crystalline precipitation. Mannich recognized the enormous synthetic significance of the reaction after seeing that the identical condensation result could be obtained by combining antipyrine, formaldehyde, and ammonium chloride in any sequence, independent of the sequence of inclusion.



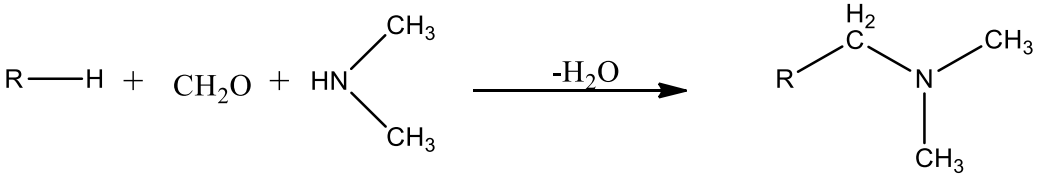
The hydrogen atom of antipyrine's carbon-4 was implicated in the process. Mannich and Kather [57] handled equal quantities of dimethylamine hydrochloride, formaldehyde, and antipyrine, yielding 4-dimethylaminoantipyrine as the base. By using a methylenic bridge, Mannich discovered that it was possible to connect two distinct chemical groups in one step. He subsequently investigated the process in great detail, with the help of a number of colleagues, and showed that it could be used to make aminomethylated compounds in general. Mannich bases have attracted an increasing amount of attention, as shown by the publication of many reviews [58-60], books [61,62], and research articles [63-81].

1.3.2. Synthesis of Mannich bases

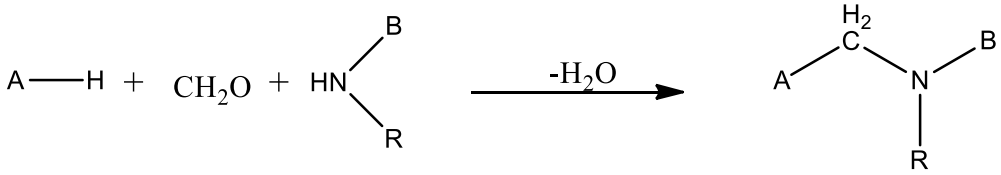
The Mannich reaction, which includes the introduction of resonance stabilised carbon nucleophiles into iminium salts and imines, is the example of carbon-carbon bond building processes. Mannich progress is a three-component abridgment of I primary amine or an ammonia or a secondary amine [82] or through amides [83]; ii)

a molecule containing an active hydrogen and iii) a non-enolisable aldehyde, typically formaldehyde [84] atom in its basic and most well-known form (substrate). These three compounds condensed through the discharge of water to form a novel base designated as a Mannich base that has an amino methyl group in lieu of the active hydrogen.

The Mannich reaction is a very important synthetic conversion since it forms together a a carbon-nitrogen connection and carbon-carbon connection during the aminomethylation step, as shown in the following basic scheme.



One step binding of different molecules



The Mannich base may be further reacted in three different forms. It can condensed by compounds containing active hydrogen, and two or one extra fragments of aldehyde depending on whether it is a primary or secondary amine. The Mannich base can condense through two or one specific components of ammonia or

amine and aldehyde if the energetic hydrogen complex contains three or two active hydrogens.

The Mannich process is a key metabolic pathway that leads to natural chemicals, primarily alkaloids. The Mannich reaction has been used to aminoalkylate aromatic substrate, which is crucial for the implementation and transformation of physiologically active molecules, according to Chi et al [85]. Because the amino group may be readily transformed into a number of different functions, it also offers easy access to several important synthetic key components [86].

As a result of the Mannich reaction's flexibility, as well as the impressive opportunities of investigating the reactivity of Mannich bases, that gives extra derivatives, it is feasible to understand and analyze the most diverse biochemical assemblies in accordance through the applied necessities and model compounds and claims. Besides the inert tertiary amine derivatives, the substrates appropriate for Mannich base production are generally accessible, and there are very few restrictions in the selection of amines across a variety of compounds.

1.3.3. Aminomethylation Reactants

1.3.3.1. Substrate

XH compounds with nucleophilic characteristics, with X= N, C, or other heteroatoms, are often used as substrates. Saturated or unsaturated compounds are

very effective in activating ‘CH' molecules. Amines and heterocycles are two examples of ‘NH' substrates. Alcohols produce stable Mannich products from ‘OH' substrates. Sulfur and phosphorous-containing substrates include sulfinic acids, thiols, phosphines, and phosphorous acid derivatives, which are XH derivatives with the ‘H' atom bound to the lower oxidation state in the hetero atom. The usage of As and Se molecules has also proven effective. Hormones, antibiotics, and alkaloids are examples of uncommon organic substances that may be used in the Mannich reaction. Chemo, regio, and stereo specific compounds may be made using a substrate containing responsive prochiral centres.

1.3.3.1.1. Amines

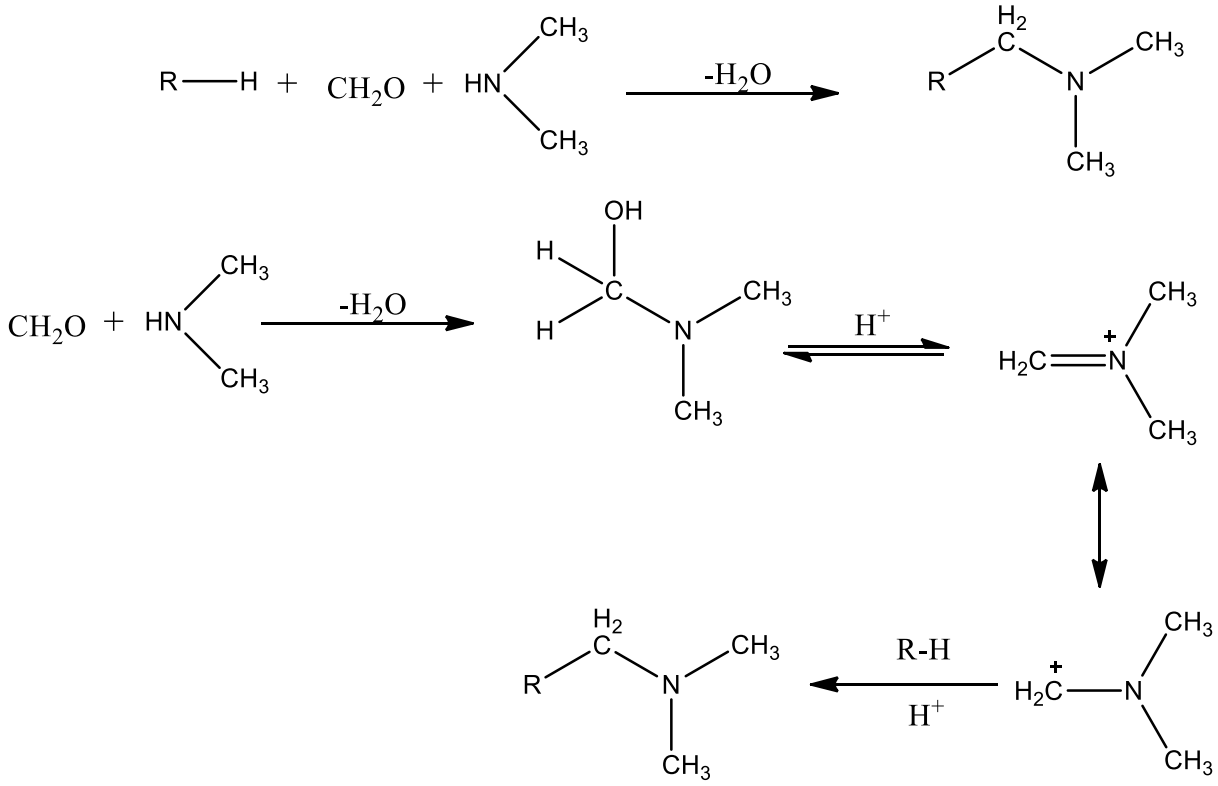
Amines with nevertheless one reactive hydrogen atom comprise N_2H_4, NH_2OH, or NH_3, compounds, along with aromatic and aliphatic secondary and primary amines, which are used more often. The same used are hetero aromatic ‘NH' analogues. In Mannich synthesis, a variety of amines have already been employed for various reasons. The steric hindrance [87,88] and the basicity of the amine are the criteria and essential characteristics for choosing the amine to conduct the Mannich reaction. When polyfunctional amines are used, unwanted by-products are produced. Consequently, when bifunctional amines like piperazine are used, bis-mannich base analogues are invariably produced [89].

1.3.3.1.2. Aldehyde

Formadehyde is frequently used in Mannich aminomethylation because it allows a methylene group to link the substrates and amine groups. Formaldehyde is commercially accessible in three types, all of which are polymeric associations that easily generate the chemical component CH_2O [90,91]. Paraformaldehyde is a linear crystalline polymer with a degree of polymerization ‘50' that depolymerizes on heating and becomes water soluble. Formaldehyde is substituted by dihalogenides of methylene CH_2XY (Y or X = I, Cl) [92,93] or ether variants like chloromethyl ether [94] under certain experimental parameters. Aminoalkylation using aldehydes apart from formaldehyde, as well as ketones [95-97], has been accomplished effectively. While using aldehydes apart from formaldehyde, meanwhile, considerations like as electronic effects and group steric hindrance must be made.

1.3.4. Mechanism

It would be difficult to provide a comprehensive method [98-104] incorporating so many distinct substrate types. The primary route of the Mannich reaction is shown in the diagram below in a broad sense: Amine combines with formaldehyde to produce a condensation artefact with both the form of a methylene ammonium salt or N-aminomethyl component, which may subsequently target the substrate RH. Spectroscopic techniques have shown the existence of aminomethylating intermediates.



1.3.5. Applications

The Mannich bases may be used to synthesize a variety of high-value pharmaceutical medicines that have an aminoalkyl backbone. Procyclidine, cocaine, ranitidine, fluoxetine, trihexyphenidyl, ethacrynic acid, atropine, [105-107], and others are significant Mannich bases that find use in the biological sector, such as those that include an aminoalkyl group. Furthermore, these bases are widely recognized for their importance in the creation of successful medicinal treatments.

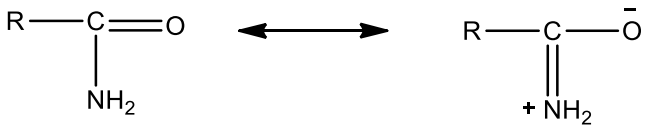
According to the literature review, Mannich bases are extremely reactive and easy to convert to other compounds; for instance, they may be reduced to produce pharmacologically important amino alcohol [108]. Mannich bases are quite well for

its anti-inflammatory [109,110], anticancer [111,112], antibacterial [113,114], antifungal [115,116], anticonvulsant [117], anthelmintic [118], antitubercular [119,120], analgesic [121], antimalarial [122], antipsychotic [123], antiviral [124] properties. Mannich bases are also utilized as detergents ingredients [125], resins, polymers, and surface active agents [126], among other applications. The stereoselective carbon–carbon bond production is catalyzed (ligand accelerated and metal assisted) using optically pure chiral Mannich bases from 2-naphthol [127]. The Mannich bases and its analogues are also useful as intermediates in the production of bioactive compounds [128,129]. This process may also be used to make key components for nitrogen-containing molecules [130]. Mannich bases are used as a stimulant for plant growth regulators in the agricultural sector [131].

1.4. Chemistry of amides

The comparative affinities of metal ions towards ligand atoms were studied extensively. The existence of the metal ion and the ligands determines the stability of coordination compounds. The heterocyclic base comprising oxygen and nitrogen donors were obviously regarded suitable ligand sites for metal atom coordination [132,133]. Complexes using nitrogen as the donor element will be more stable if they form a chelation ring. The potential of compounds with an amide moiety to produce metal complexes and show a broad array of biotic functions is extensively documented in the literature [134-142]. During complex formation using protons

and metal ions, an amide moiety provides two possible binding sites, namely via nitrogen and oxygen [143]. It is now widely recognized that both protonation and metal ion bonding occur at the amide oxygen for neutral amide groups [144]. The binding changes to the amide nitrogen [145] after deprotonation. However, due to factors like as bite size and steric barrier, coordination may indeed occur at the amide nitrogen. Amide's structure is most likely a resonance hybrid of the structure below:



The stretching province of carbonyl (amide I) at 1665 cm^{-1} of amide experiences a bathochromic change of approximately 10-20 cm^{-1} when it is coordinated via an oxygen atom, according to the vibrational spectra of amide complexes [146,147]. The amide II band, which is ascribed to assorted (N-H) in-plane bending and (C-N) stretching modes, changes to a inferior incidence at 1626 cm^{-1}. The bands at 3350 and 3180 cm-1 will emerge at higher frequencies owing to N-H symmetrical and asymmetrical stretchings. Coordination via nitrogen, on the other hand, decreased N-H stretching frequencies while increasing the amide II group frequency. As a result, if coordination occurs via carbonyl oxygen, the participation of polar form develops much more significant, and (C=O) decreases. However, if the metal is coordinated via the nitrogen atom of the $-NH_2$ group, (C=O) rises.

1.4.1. Transition metal -amide complexes

Saleeva et al [148] revealed the development of a pale green anhydrous Cu (II) complex through the configuration Cu $(CH_3CONH_2)_2Cl_2$ via an alcoholic solution. The compound has a magnetic moment value of 2.07B.M and a breakdown temperature of 110°C. The complex's ir spectra shows oxygen coordinating. There were also reports of acetamide complexes containing diphenyltin (IV) chloride and bromide and tin (IV) bromide [149]. The infrared spectrum in each instance shows acetamide oxygen coordination.

Ftir spectrum and X-ray diffraction investigations revealed that the Co(II) complexes of acetamide through the formula $CoX_2.6L$(L = CH_3CONH_2; X = ClO^{4-}, NO^{2-}, Cl^-,) were produced in non-aqueous environments [150] and described as octahedral complex, indicating acetamide coordination via oxygen atom.

Through refluxing the contents in benzene, a blue-colored solid, $NiX_2.6L$ (L = CH_3CONH_2; X = Cl^-) complex [151] was created. The infrared spectrum and the magnetic moment value (3.49 B.M) indicate that the Ni(II) ion in the complex is octahedral linked via acetamide oxygen atom.

There have been a quantity of Zn (II) complexes produced using acetamide. Through refluxing acetamide using Zn (II) chloride in an inert solvent, Paul et colleagues [152] produced a glassy crystalline complex through the formula

($ZnCl_2.2L$) (L = CH_3CONH_2), wherein vibrational spectra in the far IR region indicated M-O binding via oxygen atom of acetamide.

The coordinated ligands of acetamide complexes ($MX_2.4L$) (L = CH_3CONH_2; X = I^-, Br^-, Cl^-; M= Ni (II), Co (II), Mn (II);) have an octahedral framework wherein metal ions were linked to acetamide through the carbonyl oxygen [153].

Prabhu et al [154,155] have recently synthesized and studied novel aminobenzylated Mannich bases, namely N,N' bis (morpholinobenzyl)urea (MBU), and piperidinobenzylurea (PBU) using PMR, 13C NMR, mass spectrometry, and IR. PBU's metal complexes (MX2.L.nH2O) and (MX2L2) (X= NO3-, Br-, Cl-; n = 0,2; M = Ni (II), Co (II), Mn (II), and Cu (II)) have been characterized. The bidendate character of the ligand interacting through carbonyl oxygen and piperidyl nitrogen atoms was shown by IR and PMR spectral data.

Penland et al [156] used IR spectroscopic data to demonstrate that the metal-oxygen binding in the complexes ZnL_2Cl_2, CrL_6Cl_3, and FeL_6Cl_3 (L = NH_2CONH_2) was reduced since 1683 cm^{-1} to 1605 cm^{-1}.

Srivastava and Madhok [157] synthesized numerous (MoO_2L_2) Cl_2 molybdenum complexes using RNHCONHR' (R = p-tolyl, pyridyl, o-totyl, 5-nitropyridyl, 6-methylpyridyl, 4-methylpyridyl; R' = phenyl,), pyridylureas, wherein the ligands were coordinated to the metal over carbonyl oxygen.

Numerous studies [158-169] have been published on the coordination of modified acetamide via carbonyl oxygen. The production and pharmacological investigations of Zn(II) complexes of benzamide and nicotinamide were reported by Bajpai [170] et al. The production, pharmacological, and catalytic characteristics of Ru(II) benzamide Schiff base complexes were described by Bhowan et al [171]. Infrared spectra reveal that the coordination occurs via the carbonyl oxygen of the amide.

Because of their application as insecticides [175], stabilizers [176], analytical reagents [177], and physiologically active chemicals [178-180], the science of transition metal complexes of semicarbazones [172-174] is gaining popularity.

Semicarbazones may also act as N,O donors, forming a wide range of complexes [181,182]. Semicarbazones usually respond in the keto form [183,184], however they have recently been demonstrated to interact in the enol form following deprotonation [185,186].

1.5. Antimicrobial activity of metal complexes

The finding of disease-causing microorganisms prompted humanity to devise a strategy for eliminating microbes in and around the living activity. The quest for compounds with strong antibacterial activity becomes an important field of study in this age as a result of this push. The toxicity of chemical compounds as antimicrobes to both host and microbial cells is a significant drawback. As a result, the chemical

compounds employed should be selectively poisonous to dangerous bacteria while being nontoxic to host tissues. Some manufactured and natural substances are harmful to bacteria and fungus although not to the host mammal. When bacteria and fungi are exposed to a medication over an extended period of time, they acquire drug resistance, rendering even the most valuable drug useless. As a result, scientists must be continuously creating and evaluating novel chemicals for antibacterial efficacy.

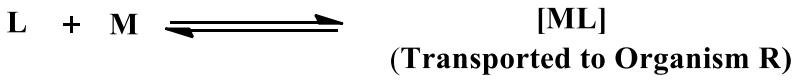
Different synthetic ligands demonstrate excellent antibacterial, herbicidal, insecticidal, and fungicidal properties [187-191]. Complexes of transition metal ions through different ligands were revealed to demonstrate antimicrobial activity in contradiction of a range of microorganisms, as well as toxic effects towards a number of cell lysis for rodents and person in cell culture.

A review of the literature reveals that biometal activity is frequently influenced by the complexation with physiologically significant chemicals [192-195].

Metal chelates serve a crucial function in biological processes where metal ions are recognized to trigger enzymes. Metal-ion-containing enzymes serve as cofactors for enzyme function [196,197]. Metals are employed for two purposes: one, to ensure correct stereochemical alignment, while the other, to drive interacting molecules closer to the enzyme's active sites so that the reactions may take place.

This should be emphasized that metals do not persist in biological systems as free metal ions, but rather as metal chelates with remarkable stability.

The steric, electronic, and pharmokinetic variables all influence the action of metal chelates [198]. The interative interactions that attach the component to the organisms determine the mode of action of an organic molecule. The strength of these forces may range from tight bond formation to van der waals Interactions. The electrostatic bonding and groove bonding processes are the most well-known of the potential methods. The compound-organism interaction depicted according to the chelate theory is as follows:



The hypothesized metalbridged organic compound-organism complex is formed when an uncontaminated organic compound (L) interacts through a particular metal ion (M) to produce chelate (ML), which drags to the creature (RML). The organic compounds' chelating capabilities are utilized to convey them over membranes or to bind themselves to a particular location, since they may inhibit bacterial growth. A variety of heterocycles have been linked to a wide range of

biological activities. Because of the existence of multifunctional units, heterocycles have antibacterial properties. The majority of them include S, O, and N, moieties that create a strain-free, six or five -membered ring and produce a 1:2 or 1:1 (metal-organic compound) chelate through physiologically essential metal ions including Fe (II), Cu(II), Mg(II), Co(II), Mn(II), and Zn(II). They're usually in squareplanar octahedral/tetrahedral geometry. The reactivity of the resultant complexes is increased since these heterocyclic ligands are complexed with metal ions [199-203].

Modifications of substituents placed on the organic portion by utilizing heterocycles and ether-O-atoms [204-206], for example, enhance antibacterial activity by increasing the basic strength and providing -electrons delocalization throughout the whole chelate rings. Those compounds have a greater potency, which is in line with the chelates' increased stability. The existence of a –C=C- bonding in an equivalent position of an amide, acid, or phenolic-OH group on the forms of metal ion interaction of the ligand increases activity by forming stable chelate rings [207-209].

AIM AND OBJECTIVE OF THE PRESENT STUDY

CHAPTER II

AIM AND OBJECTIVE OF THE PRESENT WORK

2.1. Aim

New illnesses are emerging amongst these world population in the twenty-first century as a result of advancements and modifications in style of living and living culture, necessitating the hunt for improved medicines. Synthesis has long been a crucial and fascinating aspect of organic chemistry. Scientists who must select between several modules of synthetic pathways pay close attention to organic synthesis. Any medicinal chemist's lifelong goal is to develop novel medicines that are therapeutically beneficial to humans and go through clinical trials. The overwhelming majority of medicinal medicines have carbocyclic (or heterocyclic) ring systems as their primary chemical structure.

The use of substances such as morpholine, carbazole, N-methyl piperazine, piperidine, and phenothiazine as efficient and agreeable molecules for achieving the Mannich reaction has increased over the past decade as the heterocyclic ring containing Mannich bases have been discovered to be prospective antimicrobial agents for regulating a wide range of bacteria and virus prone illnesses.

The Mannich reaction creates a new methylenic bridge between an active hydrogen molecule and formaldehyde and a primary amine or secondary amine,

resulting in the introduction of a new carbon atom. It's only a simple addition phase with no ultimate removal, which is likely due to +NH-weaker R2's releasing group than water. Mannich bases are the end products of numerous Mannich reactions and are used as synthetic intermediates in various synthetic pathways. Multi-component reactions are a significant element of modern organic synthesis, with benefits such as shorter reaction times, repeatability, and the possibility to produce physiologically active molecules. Many studies have shown that combining two (or more) heterocyclic groups in a merged or connected form greatly increases the biological activity of pharmacological compounds. The Mannich reaction has been identified to be used in organic synthesis and to be of medicinal relevance.

After evaluating all of this, we resolved to use certain substrates with active hydrogen atoms, such as 1,3-cyclohexanedione, to synthesis novel compounds via the Mannich process. Salicylaldehyde and other secondary amines such as semicarbazide, urea, and thiourea were used to make them condensed. The mannich bases have all been used as possible ligands for transition metals like iron, nickel, copper, manganese, and chromium. The disc diffusion technique was used to test the newly synthesized compounds for antibacterial and antifungal activity.

2.2. Objective of the work:

There is no report on the Mannich bases of 1,3-cyclohexanedione and Salicylaldehyde and their metal complexes, which we propose to study, according to our literature search. As a result, the current investigation's goals include

- To synthesize the Mannich bases of 1,3-cyclohexanedione and salicylaldehyde, namely,
  (a) 2-((2,6-dioxocyclohexyl)(2-hydroxyphenyl)methyl)hydrazine carboxamide (CMC)
  (b) 1-((2,6-dioxocyclohexyl)(2-hydroxyphenyl)methyl)urea (CMU)
  (c) 1-((2,6-dioxocyclohexyl)(2-hydroxyphenyl)methyl)thiourea (CMT)
- To make complexation of the so formed bases with transition metals such as Copper, Nickel, Iron, Chromium, and Manganese.
- To study the physical properties such as, melting point, color, solubility and conductance of all the synthesized ligands as well as the complexes.
- To characterize the synthesised ligands and the metal complexes by spectral methods like UV-Visible spectroscopy, FT-IR, ^{1}H and ^{13}C NMR, EPR and mass spectroscopic methods.
- To evaluate the biological activity such as antibacterial and antifungal activity against several bacterial and fungal strains of all the newly synthesized ligands (**1-3**) and the corresponding metal complexes (**1a-1e**), (**2a-2e**), (**3a-3e**).

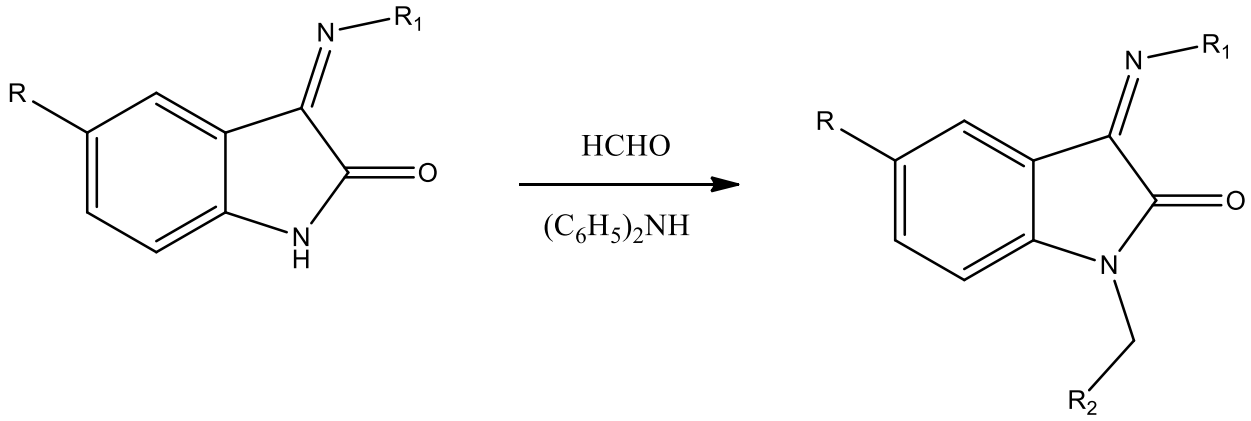
REVIEW OF LITERATURE

CHAPTER III

REVIEW OF LITERATURE

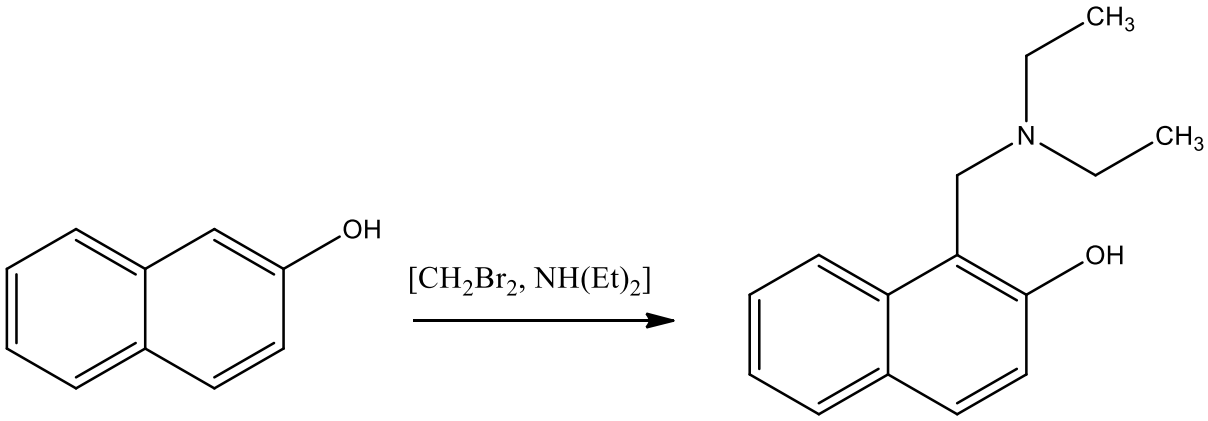
3.1. Synthesis of Mannich bases

Several researchers have mentioned different techniques in the literature for synthesizing Mannich bases utilizing a variety of intriguing substrates. Seshaiah Krishnan et al. [210] Manufactured Mannich base derivatives from isatin Schiff base compounds in the effect of formaldehyde and diphenylamine.



Scheme 1. Synthesis of Mannich base derivatives by using the Schiff bases of isatin

Mannich base was made by Yung-son Hon et al. by reacting phenolic chemicals with a warmed combination of dibromomethane and diethylamine [211].



Scheme 2. Synthesis of Mannich base derivatives from phenolic compound

Mannich bases were synthesized by N. Pandeya and D. Sriram Dave by combining the acidic position of isatin using secondary amines with formaldehyde [212]. The Mannich basis of coumarin [213] was synthesized by A.Christos Kontogiorgis et al.

3.2. Therapeutic Importance

Mannich base derivatives are related to a wide-ranging variety of biological purposes and medicinal uses, as well as the following:

1. Anti-inflammatory
2. Antifungal
3. Antitumor
4. Analgesic
5. Cytotoxic and anticancer
6. Antibacterial
7. Antipsychotic
8. Antimalarial
9. Antileishmanial
10. Tranquilizer

T. Lorand and B. Kocsis have formed numerous novel Mannich base derivatives and predictable on their effective antibacterial properties. D. D. Erol, A. Rosen, and colleagues created novel Mannich base derivatives from 6-acyl-3-(3,5-dimethylpiperidinomethyl)-2(3H)-benzoxazolones and mentioned on its biotic activity. H.M. Hassan et al. manufactured and proved antibacterial activity of several novel Mannich bases having the 1,8-napthyridine moiety.

Mannich bases were prepared from nitroxoline by M. Movrin and D. Maysinger and defined as physiologically active compounds. Acetophenone connected mono, bis, and quaternary Mannich base derivatives revealed to exhibit antifungal action by T. Ojanen and colleagues. Some anti-bacterial active Mannich

base derivatives have been synthesized and reported by Y. Li, Z. S. Yang, and colleagues.

B. Shivarama Holla et al. produced all new anthelmintic active compounds (1) and antibacterial and antifungal activity compounds (2) of Mannich base derivatives.

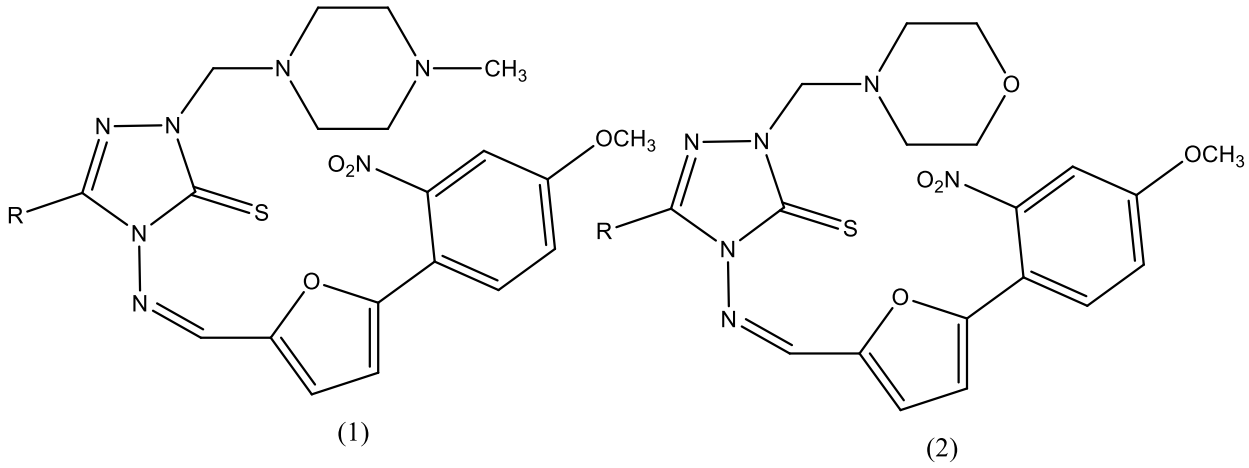


Fig. 1. Mannich bases with Antifungal Activity

In regions where chloroquine resistance is prevalent, amodiaquine and Mannich base derivatives (3) have demonstrated better antimalarial activity compared to chloroquine. As an anti-herps agent, M. L. Edwards et al. reported that the synthesis of 4-phenyl-3-buten-2-one mannich base derivatives. The pyrrole mannich base (4) has been developed by K. Malcolm Scott and colleagues as a powerful antipsychotic drug.

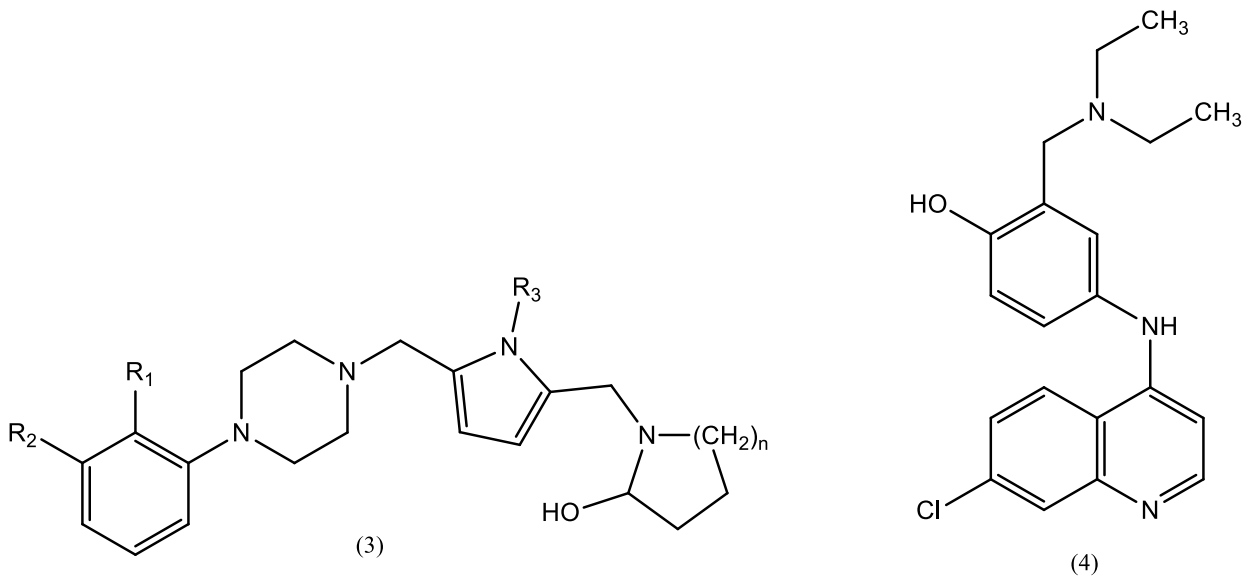


Fig. 2. Mannich bases with Antimalarial and Antipsychotic Activity

A compound (5) was the most commanding antipsychotic molecule among a sequence of aryl substituted counterparts developed by J. Knoll et al. Molindone (6), it has been revealed to have strong neuroleptic properties. The Mannich bases of chalcone exhibit cytotoxic effects, according to Jan Balzarini and colleagues.

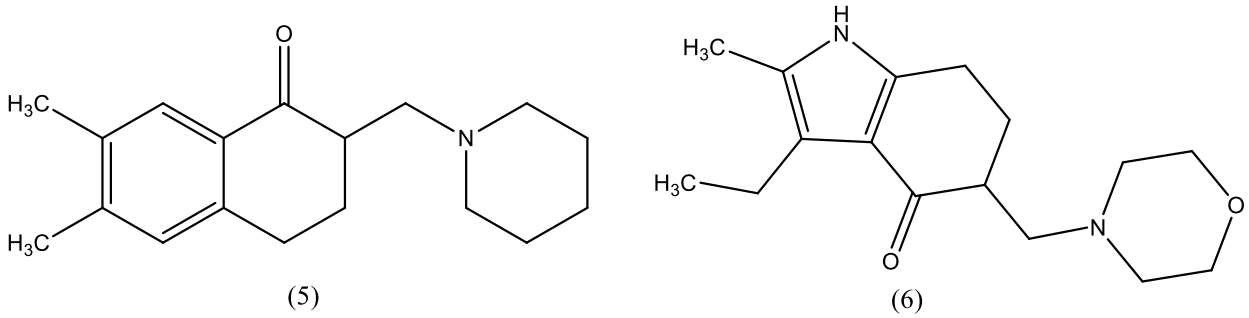
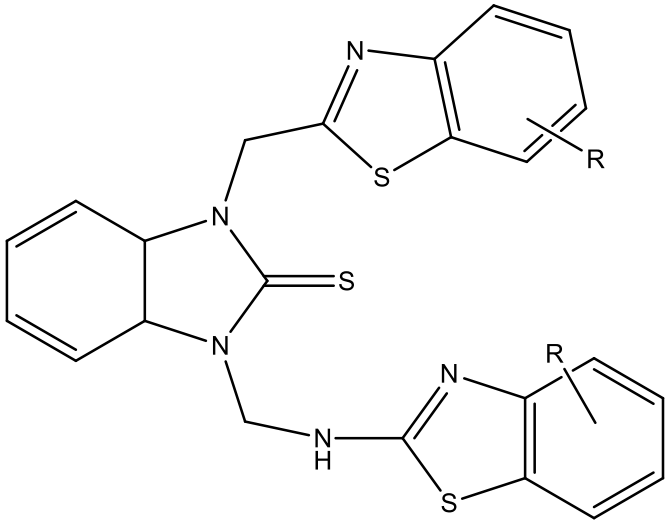


Fig. 3. Mannich bases with Neuroleptic Activity

H. I. Gul et al. discovered antifungal activity in bis Mannich bases generated from acetophenones, as well as anticonvulsant action in certain mono Mannich

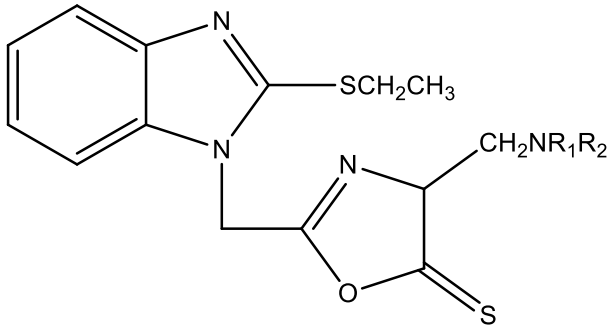
bases. Mannich bases have been identified by M. S. Shingare et al. for their production and antiviral activity (7).



(7)

Fig. 4. Mannich bases with Antiviral Activity

Compound (8) has been produced by S. Vijayraghavan et al. for antibacterial action (8).

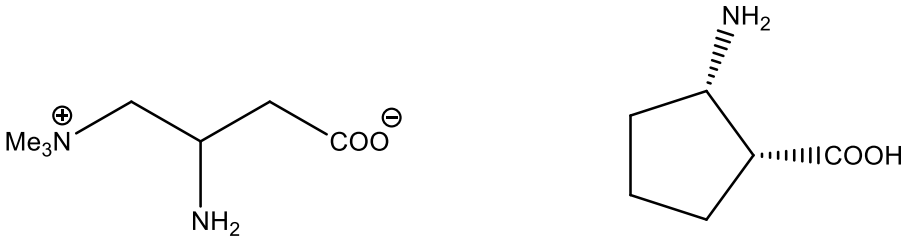


(8)

Fig. 5. Mannich bases with Antibacterial activity

The Mannich reaction is a well-known technique for making -amino carbonyl compounds and, as such, a crucial carbon-carbon link construction method in

organic synthesis. Scientists have long been inspired by this reaction's flexibility and promise to generate both structural and functional variety. The Mannich process, for instance, has been effectively used as a critical stage in natural substance production and medicinal chemistry on many occasions. β-amino acids, as particularly, are among the most significant compounds produced by Mannich processes. They frequently have significant pharmacological characteristics in their natural state. For example, while taking emeriamine orally, rats showed hypoglycemia and anti-ketogenic effects, while cispentacin is an antifungal antibiotic. β-Amino acids are however key parts of bioactive compounds like taxol, amongst the most effective anticancer medicines, that has phenylisoserine as a side chain, and antibiotics like cyanovinfin RR, nodularin, and microcystin LR, which include the unsaturated β-amino acid ADDA.



Emeriamine Cis-pentacin

Fig. 6. Compounds with hypoglycemic Activity

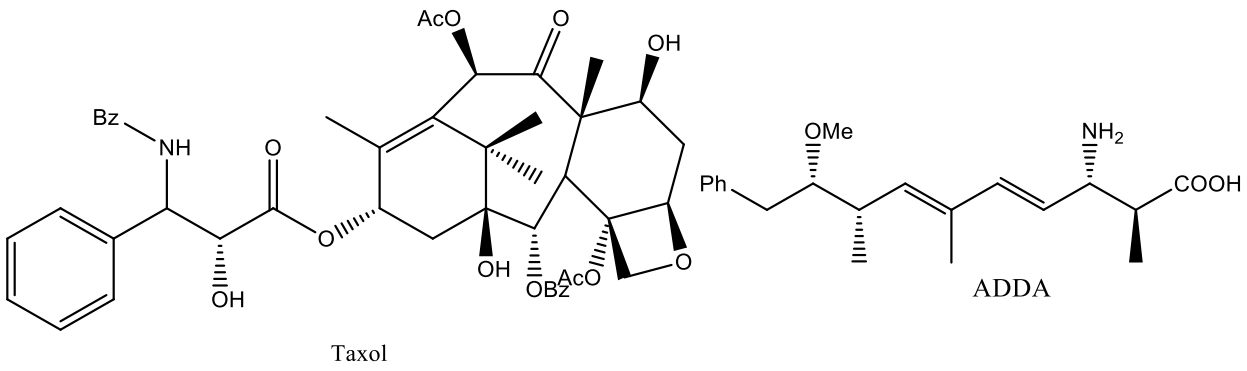


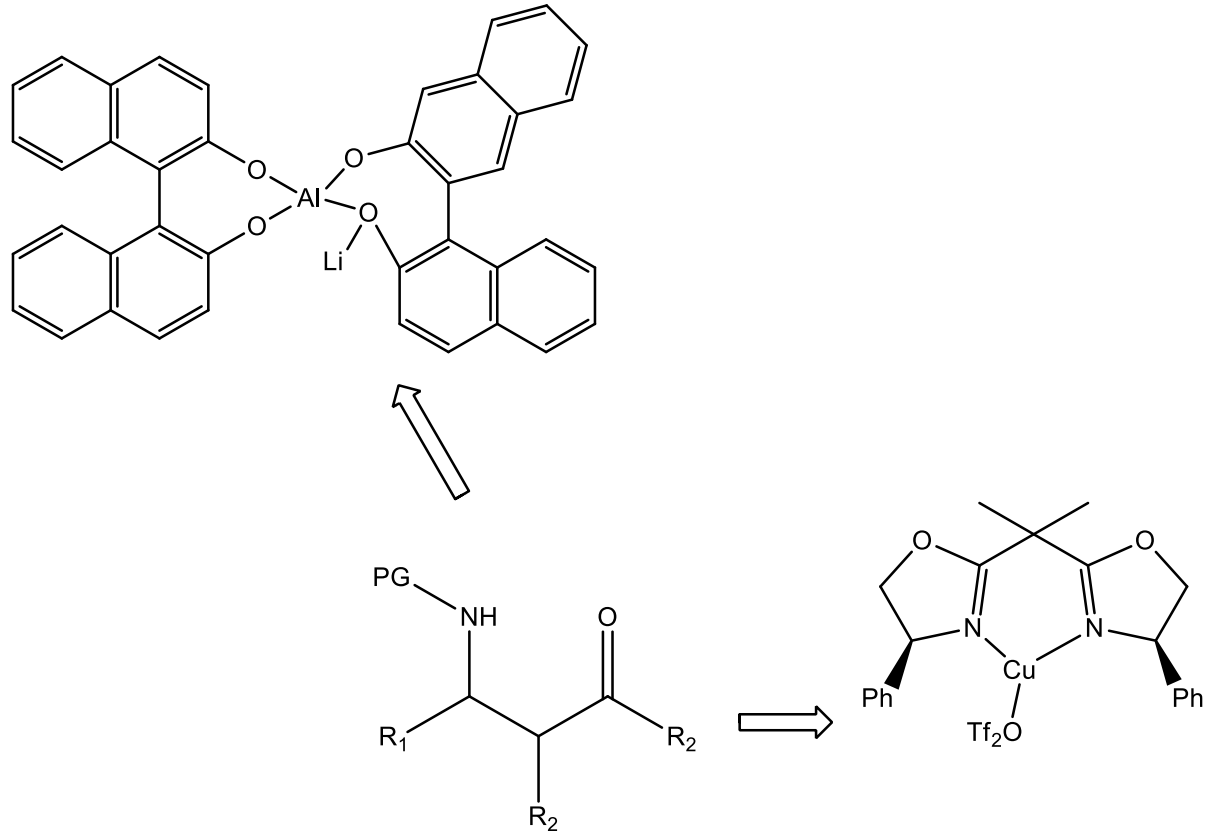
Fig. 7. Anti Tumour Agents

Even though Mannich process was already recognized for over a century, the teams of Kobayashi, Sodeoka, Lectka, and Jacobsen became the first to describe effective catalytic asymmetric additions of prefabricated enolates to imines. As a result, catalytic asymmetric Mannich base class reactions, in catalytic cycle the nucleophilic enolate is produced and investigated. Metal-free organic catalysis and organometallic complexes are used to accelerate the reactions. In terms of application and specificity, the various catalysts are complimentary.

We highlight current advances and discoveries to this study in this section. Shibasaki revealed the first instances of direct catalytic asymmetric Mannich reactions employing Al-Li-bis(binaphthoxide) (ALB) in 1999, with moderate enantio-selection and an iminium ion used as electrophile and acetophenone as contributors.

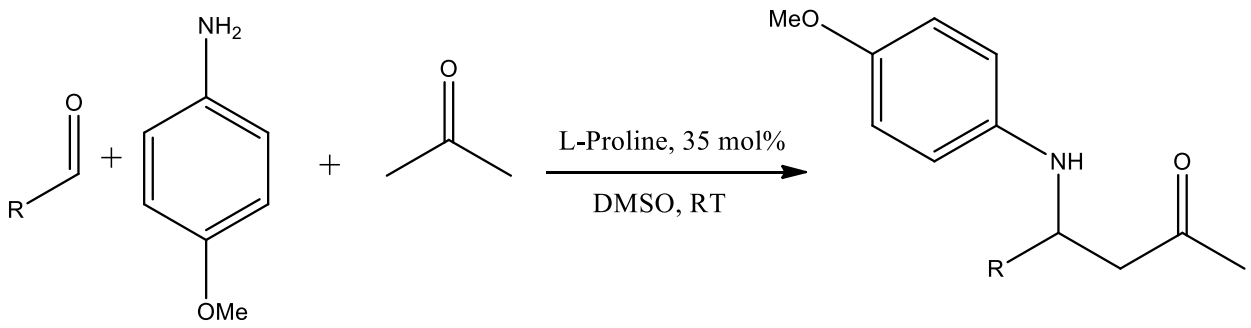
Subsequently, Jrgensen and colleagues produced a chiral bisoxazoline copper (II) complex that catalyzed from a direct asymmetric process. They also possible to

manufacture Mannich compounds with excellent yields and stereoselection by adding pyruvate analogues to imines made from glyoxalate using this method. Trost et al. obtained high diastereo selectivity and excellent enantiomeric excesses using dinuclear zinc complex among o-hydroxy acetophenone and N-PMP imine of glyoxalate in mannich base reaction 2003.



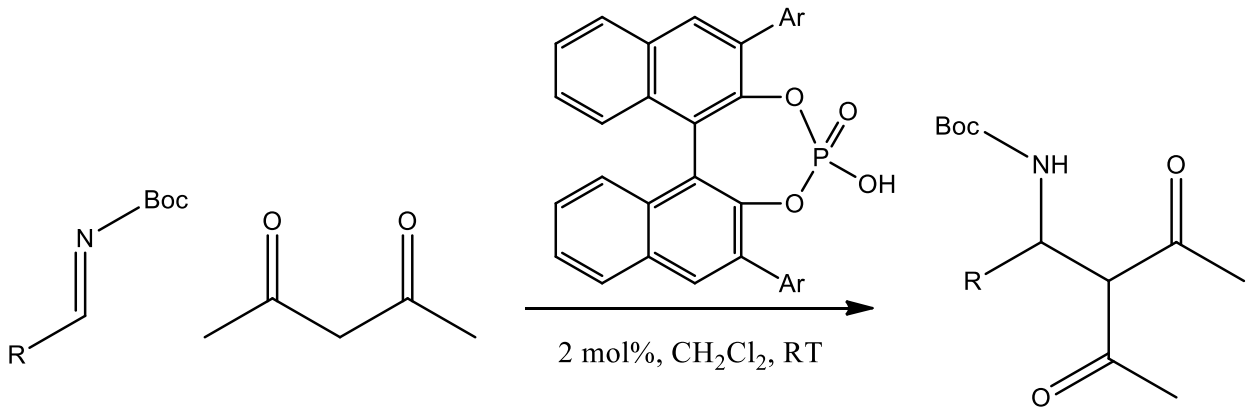
Scheme 3. Direct asymmetric Mannich reaction by Metal catalyst

List published that organocatalytic Mannich base reaction utilizing the catalyst L-proline in 2000 was the first evidenced that the metal catalyst free for the Mannich base reaction.



Scheme 4. Enantioselective Mannich base reaction by using L-proline catalyst

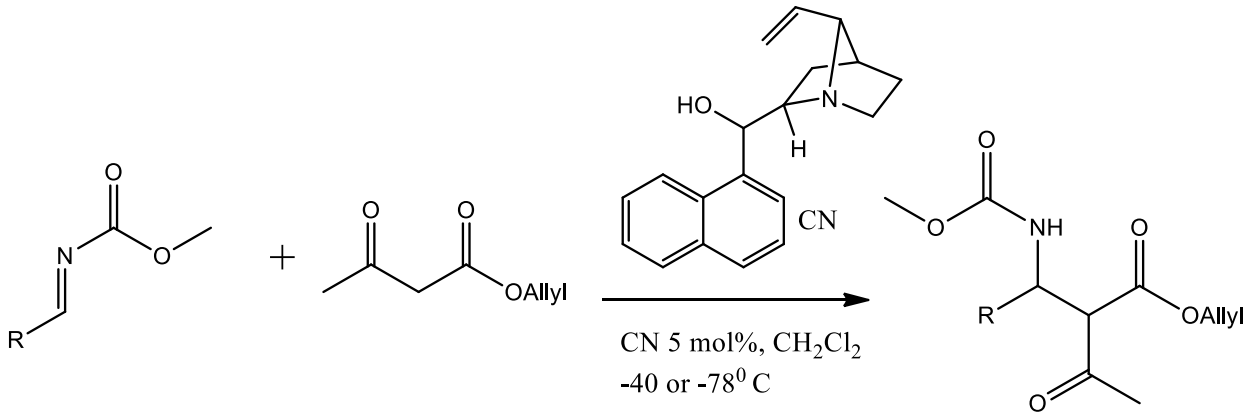
Despite the 35 mol% catalytic dosage used to give excellent yields and enantioselectivity had been achieved. Acetone reacting with catalyst to produces an enamine (nucleophile), which interacts with an electrophilic imine produced in situ in this three-component process. Terada developed chiral Bronsted acid, which was used to attach acetylacetone to N-Boc imines in 2004.



Scheme 5. Mannich reaction by using Phosphoric acid catalyst

Good yield and enantioselections were obtained with minimal catalyst loading, which was noteworthy (2 mol percent). The catalyst activates the imine from enolisable acetylacetone in this instance via H-bonding the azomethine

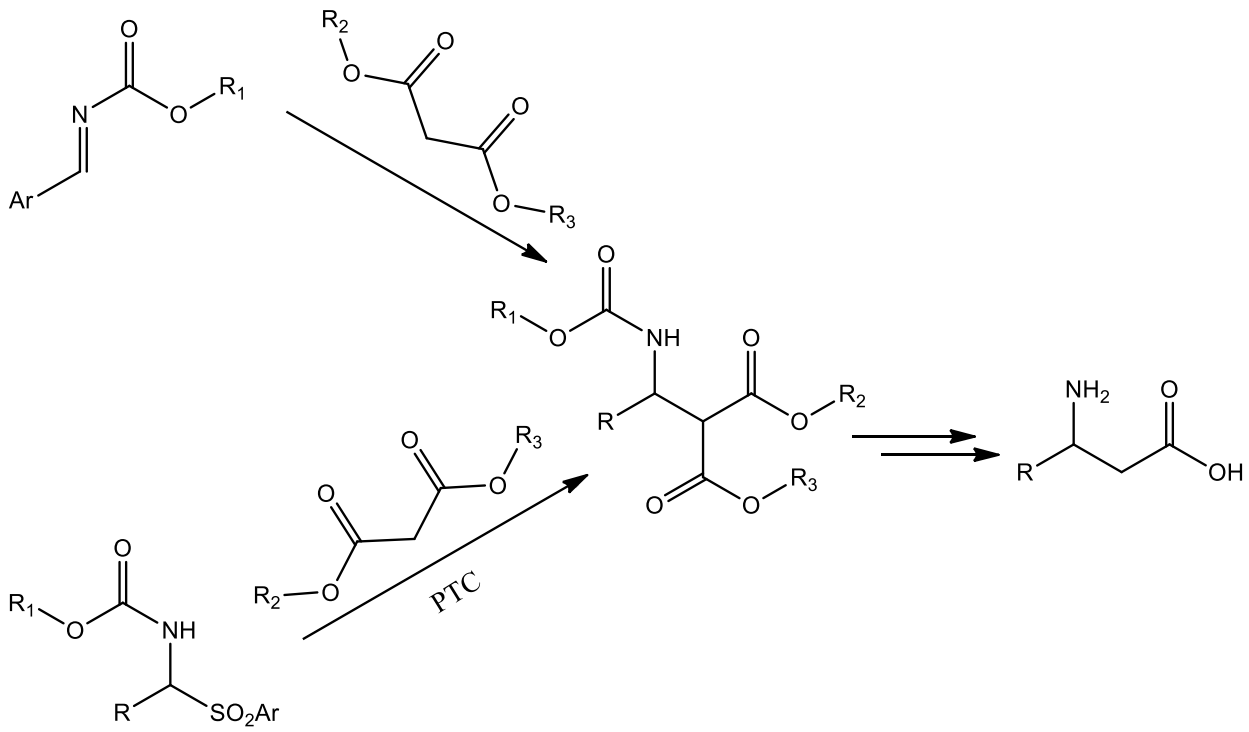
nitrogen. Synthesis of diastereoselective Mannich base derivatives from β-keto esters by using cinchonine-catalyst was reported by Schaus and coworkers.



Scheme 6. Preparation of Mannich reaction by *Cinchona* alkaloid catalyst

The chiral base deprotonates the β-ketoester, resulting in a chiral ion pair that interacts well with extremely electrophilic imine. Although with abundant and inexpensive CN, high yields could've been achieved, and the reactions with CD produced the opposite enantiomers having excellent stereoselections.

Despite the good findings published over these years, we were surprised to find no catalytic direct Mannich reactions of malonates using simple imines since we first began studying the reaction. In reality, the Mannich reaction involving malonates is crucial since the reaction's products are from three amino acids.

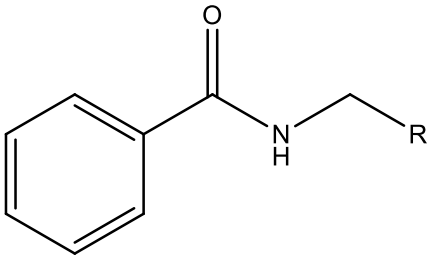


Scheme 7. Direct catalytic mannich base reaction of malonates

Synthesis of novel benzamide modified Mannich bases **9(a-c)** (Fig. 8) was tested in anti-bacterial activity towards *P. aeruginosa*, *S. aureus*, *E. coli*, and *E. faecalis*. The amoxicillin and cefixime as reference medicines for comparability were used in the test tube dilution technique. The findings were expressed as a minimum inhibitory concentration (MIC).

Among the benzamide related Mannich base derivatives the compounds **9a**, **9b**, and **9c** were shown to be the most active compounds, with MIC values that were similar to those of the conventional antibiotic's amoxicillin (1.56, 1.56, 3.125, and 3.125) and cefixime (6.25, 6.25, 12.5, and 6.25). With anti-bacterial activity result, compound 1c was shown to be the most active (3.125, 3.125, 3.125, and 6.25). These

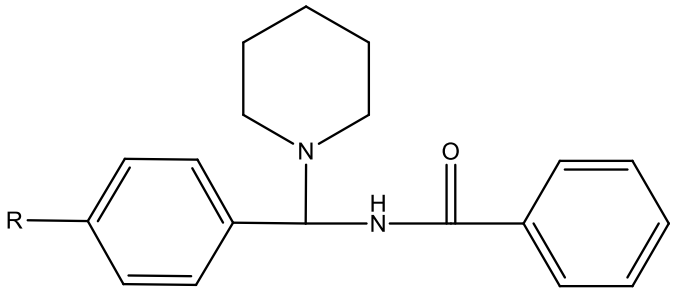
findings demonstrated that sulphonamide (9a), p-nitro (9b), and dinitro (9c) group replacements improve antimicrobial property [214].



(9a-c)

Fig. 8. Benzamide substituted Mannich bases

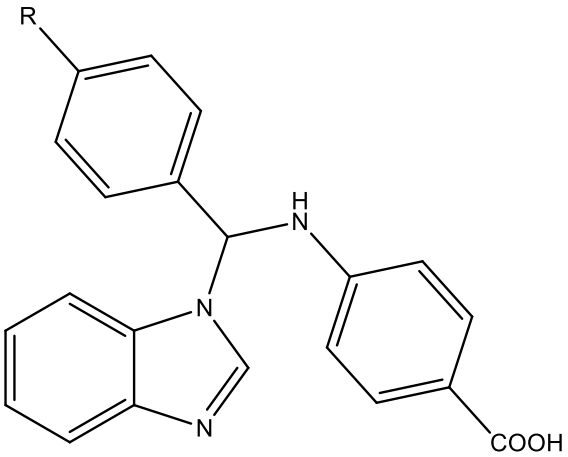
The Mannich base derivatives of modified N-[(1-piperidinobenzy)benzamide], (10a-e) (Fig. 9) have been produced. By utilizing the well diffusion technique and ampicillin as a reference drug, the antibacterial activity of produced PBB was tested on the bacterial pathogens like *P. aeruginosa*, *E. coli*, *B. subtilis*, and *S. aureus*. 2d and 2e Compounds were highly active than the standard drug Ampicillin. In this result showed that adding an electron withdrawing group to the phenyl ring increases activity while adding an electron releasing group decreases activity when compared to an phenyl ring [215].



(10a-e)

Fig. 9. Substituted N-[(1-piperidinobenzy)benzamide

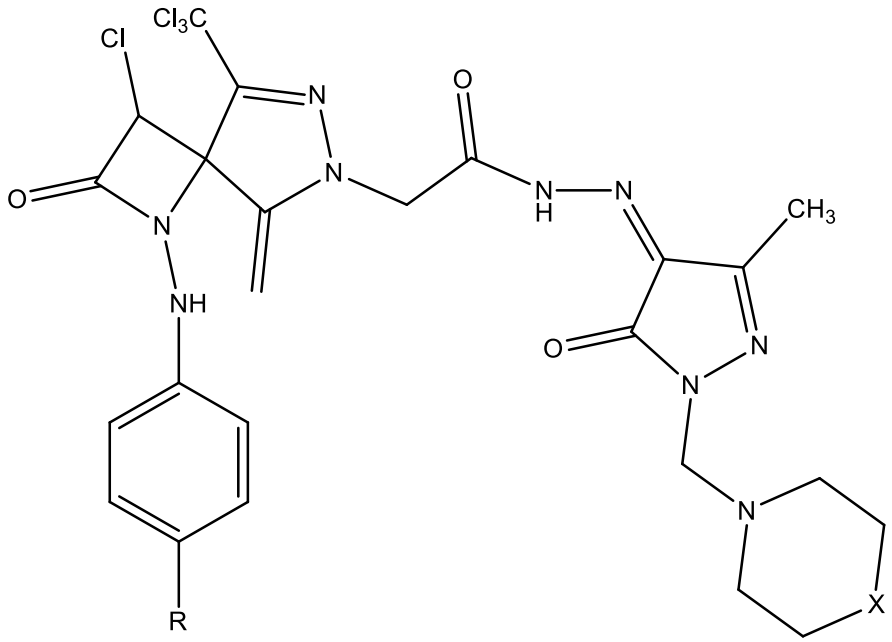
The mannich base derivatives of 4-[1H-benzimidazole-yl benzal - methyl-amino] benzoic acids (11a-c) (Fig. 10) were tested for anti-microbial activity towards , *C. albicans*, *S. typhi*, *S. aureus*, *E. coli*, *A. niger*, and *B. subtilis* accordingly. The findings were calculated using MIC values. Compounds 3b and 3c have the best antibacterial action compared with Ciprofloxin, while compound 3a showed the best antifungal activity compared to standard drug Ketoconazole [216].



(11a-c)

Fig. 10. Synthesis of 4-[1H-benzimidazole-yl(Substituted benzal) methyl-amino] benzoic acids derivatives

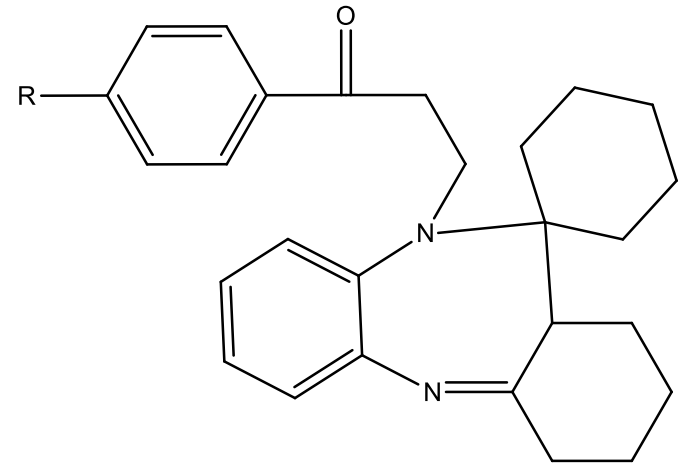
An innovative synthesis of compound 12 (Fig. 11). The compounds were tested for anthelmintic activity against *P. posthuman* compared to standard drug piperizine citrate. Compound 12 showed that highly active because of it containing the N-methylpiperazine moiety [217].



(12)

Fig. 11. Mannich bases with Antihelmintic Activity

The anticonvulsant activity of two series of 1,5-benzodiazepines 13, 14(a-c) Mannich base derivatives was tested using an isoniazid and thiosemicarbazide activated convulsion model (Fig. 12 and 13). Compound 13a shown highly active compound compared to others. The compounds 13b, 14b, and 14c were shown least active compounds [218].



(13a-c)

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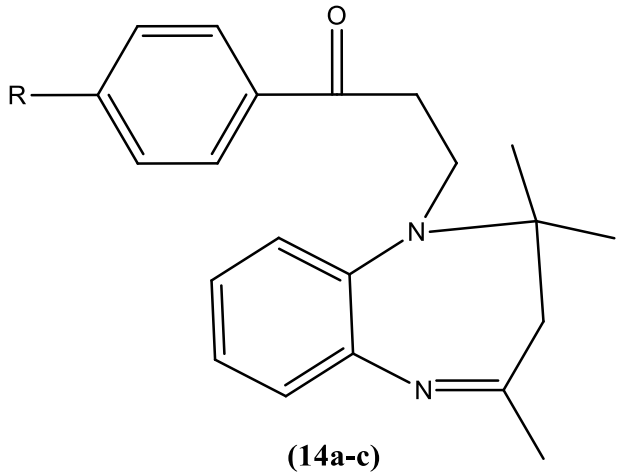
Fig. 12. Synthesis of 1,5-benzodiazepines derivatives

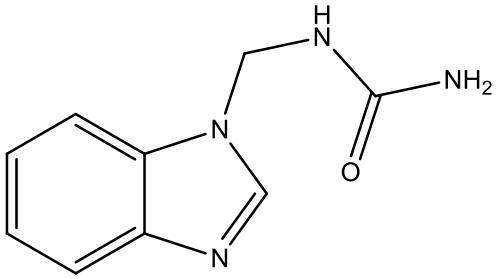


(14a-c)

Fig. 13. Mannich bases with Anticonvulsant Activity

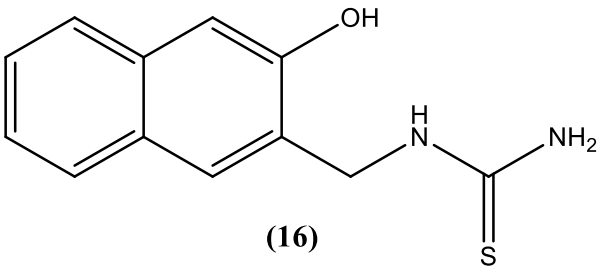
The antioxidant activity of benzamide connected mannich base derivatives, such as compound 15 (Fig. 14) and compound 16 (Fig. 15) was evaluated. The usual medication was ascorbic acid. Compounds 15 and 16 showed highly active due to presence of electron-releasing amide group in it. The benzimidazole connected to

the amide group by two nitrogen atoms , compound 15 was shown to be more effective than compound 16 [219].



(15)

Fig. 14. Synthesis of 1-((1H-benzod] imidazole-1-yl)methyl)urea compound



(16)

Fig. 15. Synthesis of 1-((3-hydroxynaphthalen-2-yl)methyl)thiourea Mannich base compound

3.3. Biological Importance of Mannich Bases

Anticonvulsant, CNS depressive, anthelmintic, insecticidal, antipsychotic, cytotoxic, antibacterial, antifungal, anti-inflammatory, local anesthetic, and antimalarial actions are among the pharmacological characteristics of Mannich bases [220]. Several Mannich bases outperform its source compounds in terms of antibacterial activity.

Anticancer action is found in Mannich bases generated from chalcones and similar chemicals. When enones are joined to intracellular thiol-containing moieties, this results in the production of enones. 2-dimethylamino-methylbenzosuberone methiodide, a Mannich base chemical, has been found to have considerable efficacy [221] towards human tumor cell lines and also murine p388 cells [222]. The antimalarial action of the Mannich bases of 7-chloroquinoline has been studied, and one of the compounds, amodiaquine [223,] has been shown to be effective. 2-(N-arylaminomethyl)-5-(E)-pentylidene cyclopentanone mannich base derivatives, as well as its structural isomers, have anti-inflammatory properties [224].

An antidepressant medication like Fluoxetin, antipsychotic drug benzoquinamide, ranitidine as a H2-receptor antagonist, and trihexylphenidyl hydrochloride, an antispasmodic drug has all been manufactured by Mannich base reaction.

Bhawser et al [225] reported that the synthesis of mannich base compounds 8-[(6'-substituted-1',3'-benzothiazol-2'-yl)aminomethyl] modified hydroxycoumarins. Antimicrobial effect towards *A. brassicicola*, *F. Udam*, *S. Aureus*, and *E. Coli* has been evaluated. The Mannich reaction yielded 4-[2-(2'-furyl) vinyl] 7-hydroxy-8-(aminomethyl substituted derivatives) coumarins have been investigated for antibacterial activity by substituting phenylpiperazines and other secondary amines with various amino acids [226].

Devki et al. [227] made Mannich bases out of 7-hydroxy coumarins and evaluated them for antibacterial activity. Patnaik et al [228] produced Mannich bases with secondary amines like thiazoles and benzimidazoles including piperidine, phthalimide, quinazolin-4-ones, and morpholine. All newly produced mannich base compounds were tested for fungicidal activity against standard drug Curvularia.

Sridhar et al [229] investigated the anticonvulsant efficacy of Mannich bases of isatin connected hydrazones using maximum electro shock (MES) at different dosages of 30, 100, and 300 mg/kg. These chemicals' neurotoxicity has also been studied. Several suitably modified 4-(dialkyl-aminoalkyl) steryl-alkyl ketones were synthesized from Mannich base reaction by Niharika et al [230]. The compounds' spermicidal efficacy has been tested. At concentrations between 0.005 and 0.1 percent, many substances showed spermicidal action.

Malimka et al. [231] identified 2H-4,6-dimethyl-2[(4-phenylpiperazin-l-yl)methyl]-3-oxo-2,3-dihydroisothiazolo[5,4,6]pyridine compound synthesized from mannich base reaction and that has a strong anarectic effect in animal models due to serotonergic system activation. A novel set of Mannich reaction prepared from formaldehyde, diphenylamine and indole-2,3-dione. All the newly synthesized mannich base compounds were tested for antibacterial activity against different strains of microorganisms by using paper disc diffusion method. The active

substances' MIC were found. From this anti-bacterial result showed that the Mannich bases was most active [232] than that of the Schiff bases.

Mannich base compound of 3-substituted-4-[5-(2,4-dichlorophenyl)-2-furfurlidine]-amino-5-mercapto-1,2,4-traiazoles was synthesized and tested for antibacterial, antifungal, and herbicidal activities have been reported by Sivarama Holla et al. [233]. The cytotoxic effect of different types of mono- and bis-Mannich bases generated from acetone towards Jurkat and Renca cells was investigated by Incigul et al [234], who discovered that converting mono to bis-Mannich base derivatives significantly improved cytotoxic activity in maximum occurrences.

Synthesis of norflaxacin via Mannich base reaction prepared from formaldehyde and various isatin analogues and tested them *in vitro* for, antibacterial, antifungal, and anti-HIV activities against HIV-1 replication in MT4 cells have been reported by Pandeya et al [235].

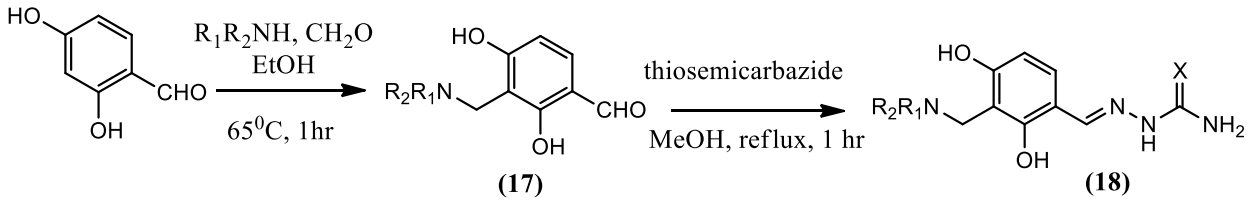
3H-pyrrolo [3, 2-f] quinoline of aminoalkylated mannich base compound have been reported as possible vaso relaxants by Mariya et al [236]. Pandeya et al [237] used 3-amino-2-methyl-mercaptoquinazoline-4(3H)-one to make Mannich bases of isatin analogues, which they tested for antibacterial action against harmful bacteria and fungi, as well as anti-HIV activity against HIV-I replication in MT4 cells. Isatin variants with N-[4-(4-chlorophenyl)thiazol-2-yl]thiosemicarbazide mannich base compounds [238] was tested for anti-HIV activity against HIV-1

replication in MT4 cells, anti-bacterial activity against 26- bacterial strains, and 8-pathogenic fungi.

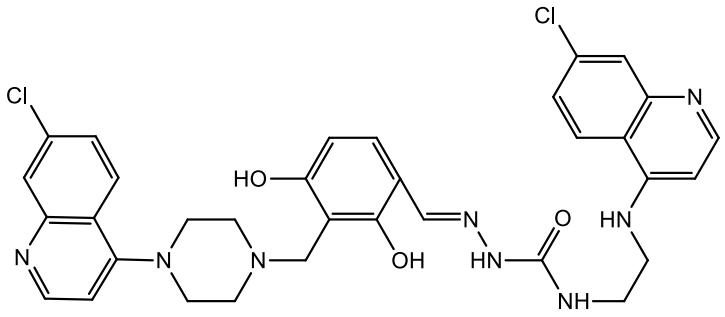
3.4. Applications of biologically active Mannich Base Compound Synthesis

3.4.1. Antimalarial active compound synthesis

Malaria outbreaks may be managed by blocking, a sulfur-containing enzyme such as cysteine proteases that the pathogen uses to hydrolyze hemoglobin. Because of the α, β-unsaturated ketones released through deamination to give highly active phenolic Mannich base compounds. In thiols, α, β-unsaturated ketones have a high affinity to it, they may selectively bind to and disrupt cysteine proteases. Chipeleme et al. reported that compound **17** prepared from formaldehyde and secondary amine with 2,4-dihydroxybenzaldehyde in the presence of ethanol medium (Scheme 8). The phenolic Mannich base compound was then transformed into the aminoquinoline semicarbazone equivalents and (thio)semicarbazole **18**. The mannich base compound of 4-aminoquinoline semicarbazones efficiently inhibited falcipain-2, a cysteine protease found in Plasmodium falciparum, whereas the mannich base compound was bisquinoline semicarbazone **19** [239] showed excellent antimalarial efficacy at IC_{50} of 0.07 μM against that chloroquine-resistant Plasmodium falciparum strain.



(17) **(18)**

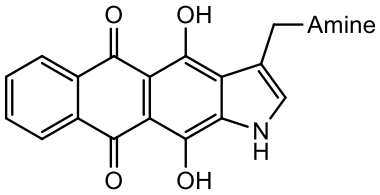


(19)

Scheme 8. Preparation of quinoline semicarbazone Mannich base compound

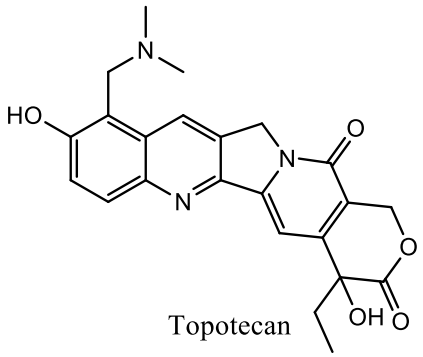
3.4.2. Synthesis of Antitumour Molecules

The rate of success of cancer treatment is limited by extremely drug-resistant tumor cells. Multi-drug tolerance in tumor cells is caused by the administration of doxorubicin, an anthracycline chemotherapy agent. Mannich base **20**, a synthetic derivative of the anthracycline 4,11-dihydroxynaphtho[2,3-f]indole-5,10-dione, demonstrated considerable efficacy against anti-tumor cell lines.

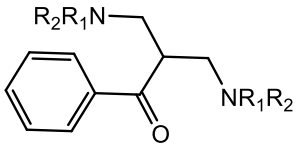


4,11-dihydroxynaphtho[2,3-f]indole-5,10-dione

(20)

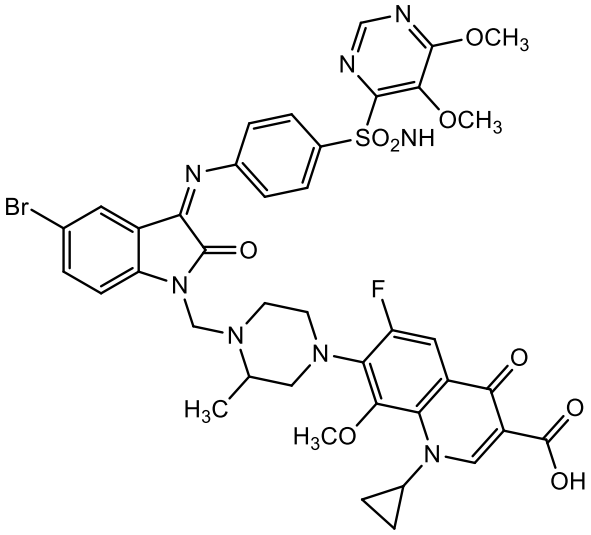


Topotecan



Acetophenone

(22)



gatifloxacin **(21)**

Fig. 16. Antitumour Mannich Derivatives

An aminoalkylated Mannich side chain containing compounds have the capacity that they are water soluble anti-tumour agents [240]. (Fig. 16). When compared to the conventional anticancer medication etoposide, the gatifloxacin Mannich analogues **21** exhibited outstanding anticancer efficacy (Fig. 16). Mannich variants **22** of acetophenone have excellent action towards Jurkat cell lines (Fig. 16).

3.4.3. Preparation of Antimicrobial Compounds

To combat the rising number of multidrug-resistant (MDR) bacteria, new antimicrobial drugs must be developed. Multiple processes working in bacteria render them extremely resistant to commonly employed antibacterial medicines, necessitating the development of next generation antibiotics to circumvent the drug resistance mechanisms. The Mannich process has been used to make a variety of antibacterial compounds. The antibacterial activities of unsaturated Mannich ketones were investigated by Lorand et al. [241]. (Fig. 17).

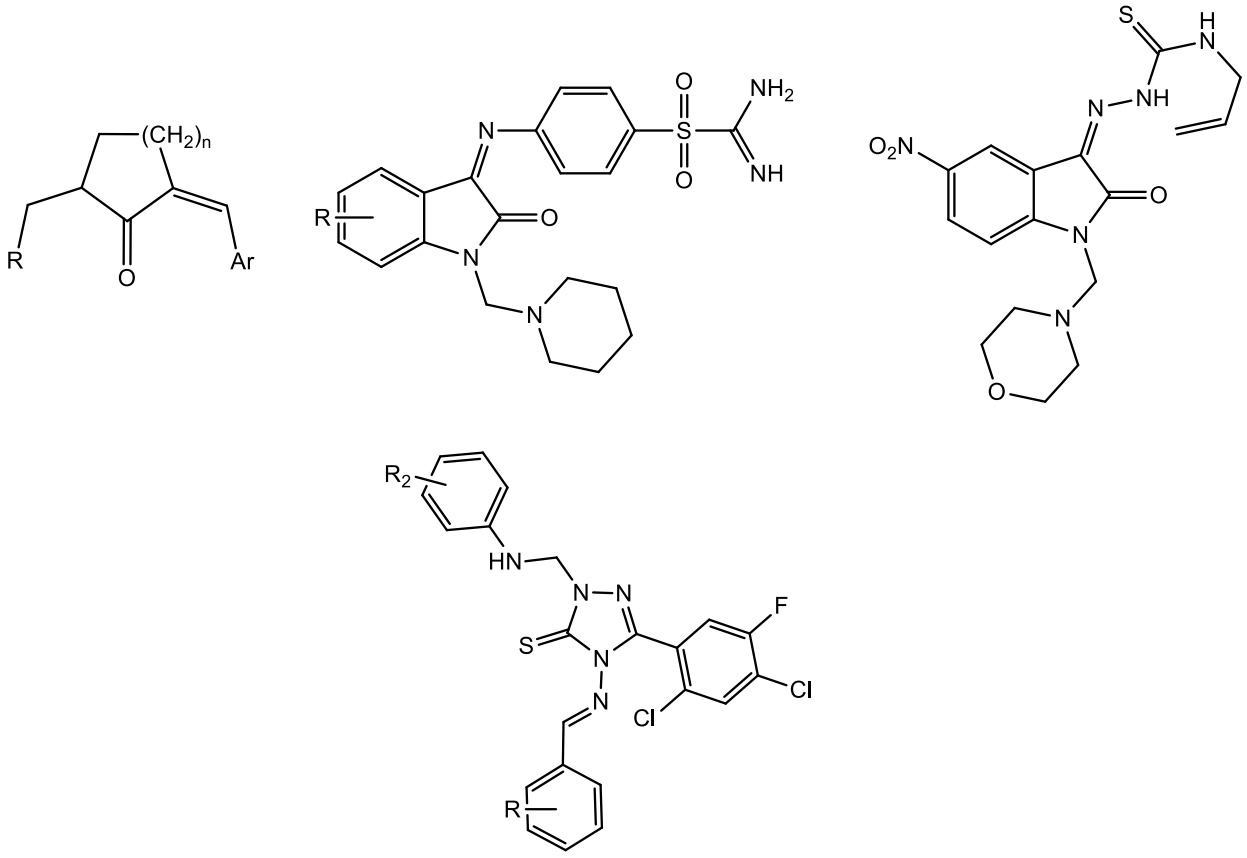
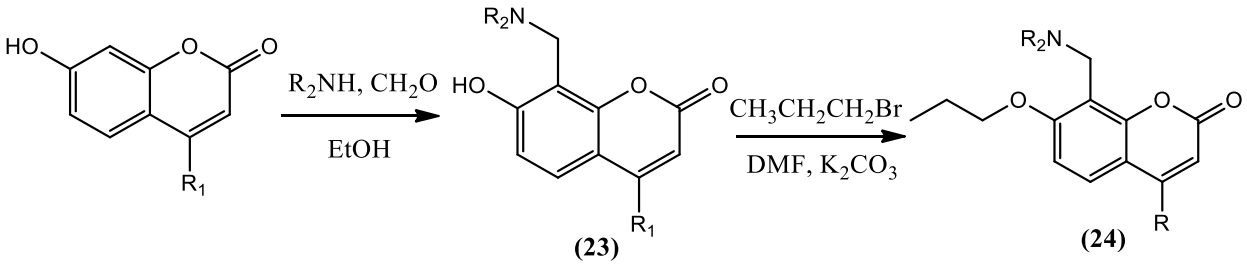


Fig. 17. Representative list of Antimicrobial agents

The inclusion of a Mannich side chain enhances the unsaturated Mannich ketones' water solubility. As a result, the Mannich analogues are more powerful than that of the parent compound and are readily delivered to the site of action. Furthermore, the antibacterial active Mannich derivatives had very low cytotoxicity, which is an important criterion for a compound to be the appropriate alcohol. This resulted in a substantial reduction in antibacterial activity.

The synthesis of Mannich base compound **23** and investigation of anti-viral activity and associated with propyl ether analogue in it. Which was described by Mazzei et al. [242]. (Scheme 9). The Mannich compounds having free hydroxyl functionality **24** had minimal antiviral effect upon hepatitis C surrogate viruses, which is noteworthy to note. Especially Mannich ether derivative **24** has effective antiviral properties.



Scheme 9. Synthesis of Antiviral active Mannich base compounds

Quinazoline thione, carboxyamide and acetophenone connected mannich base compounds **25**, **26** and **27** were tested against antibacterial action (Fig. 18). The Mannich equivalents **27** have better antifungal action than the amphotericin B standard drug.

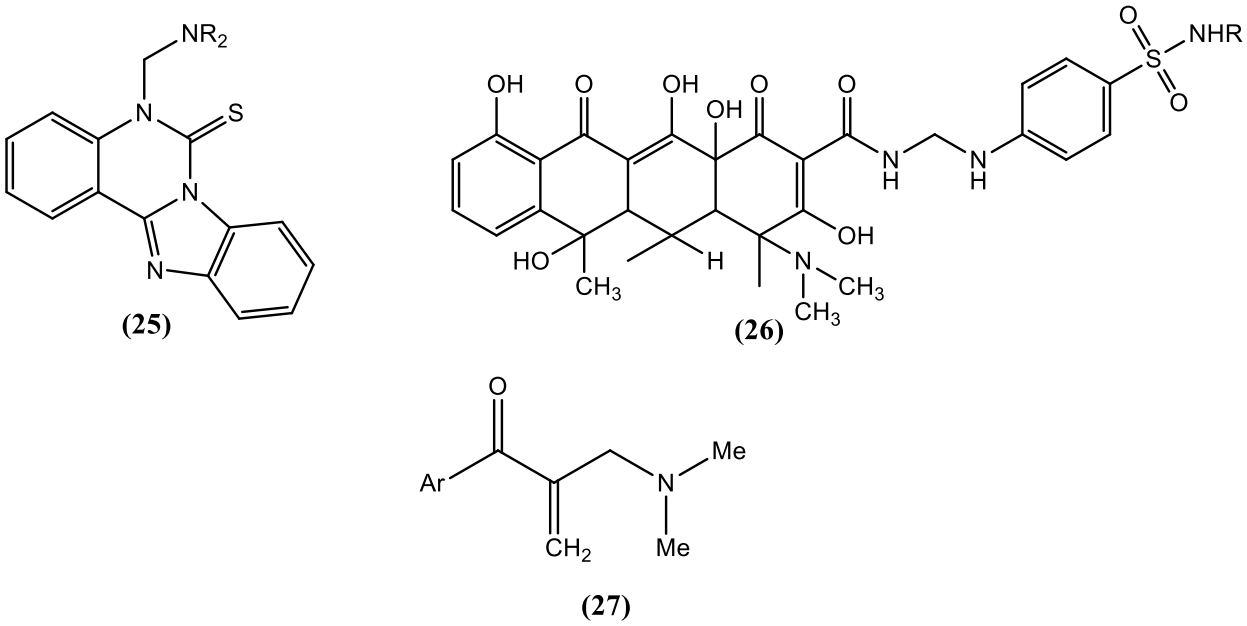
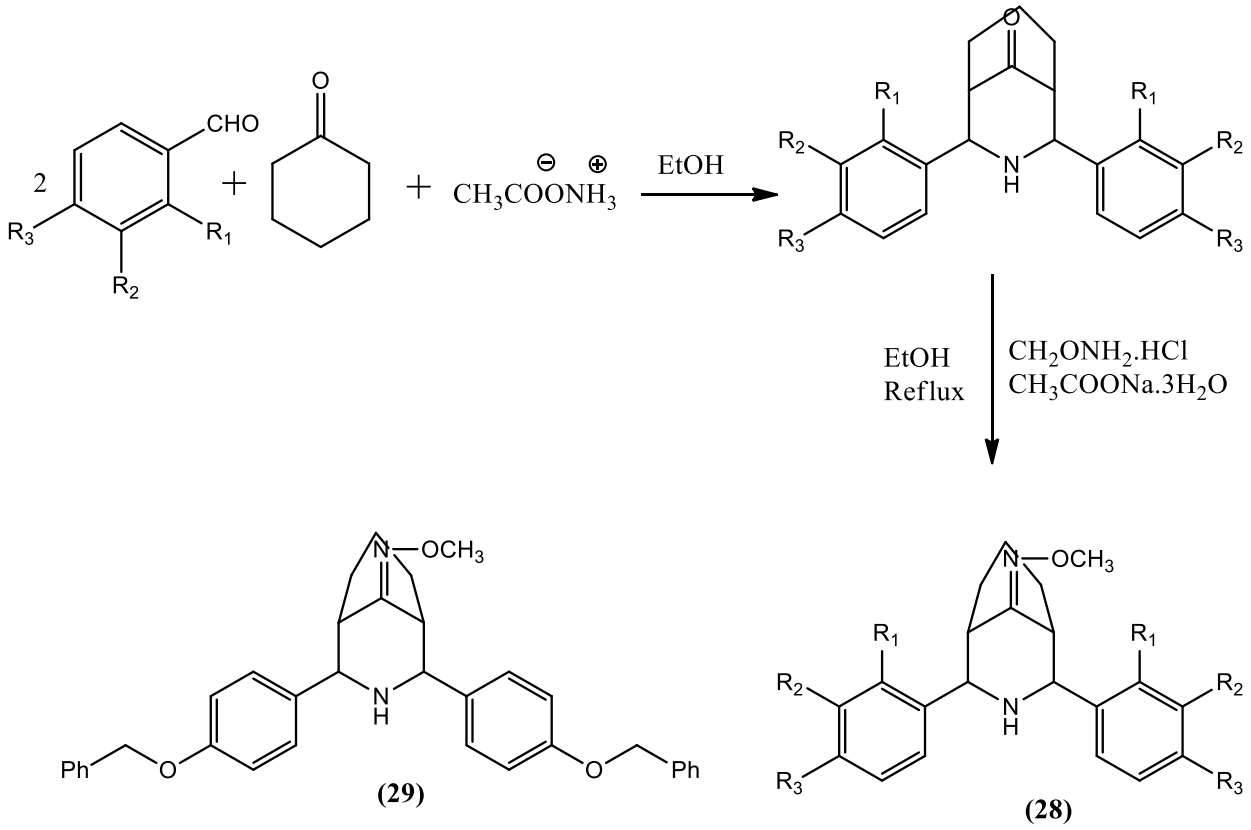


Fig. 18. Synthesis of Antimicrobial molecules from mannich base reaction

Parthiban et al. described the synthesis of mannich base compound **28** and their related N-methyl analogs [243].

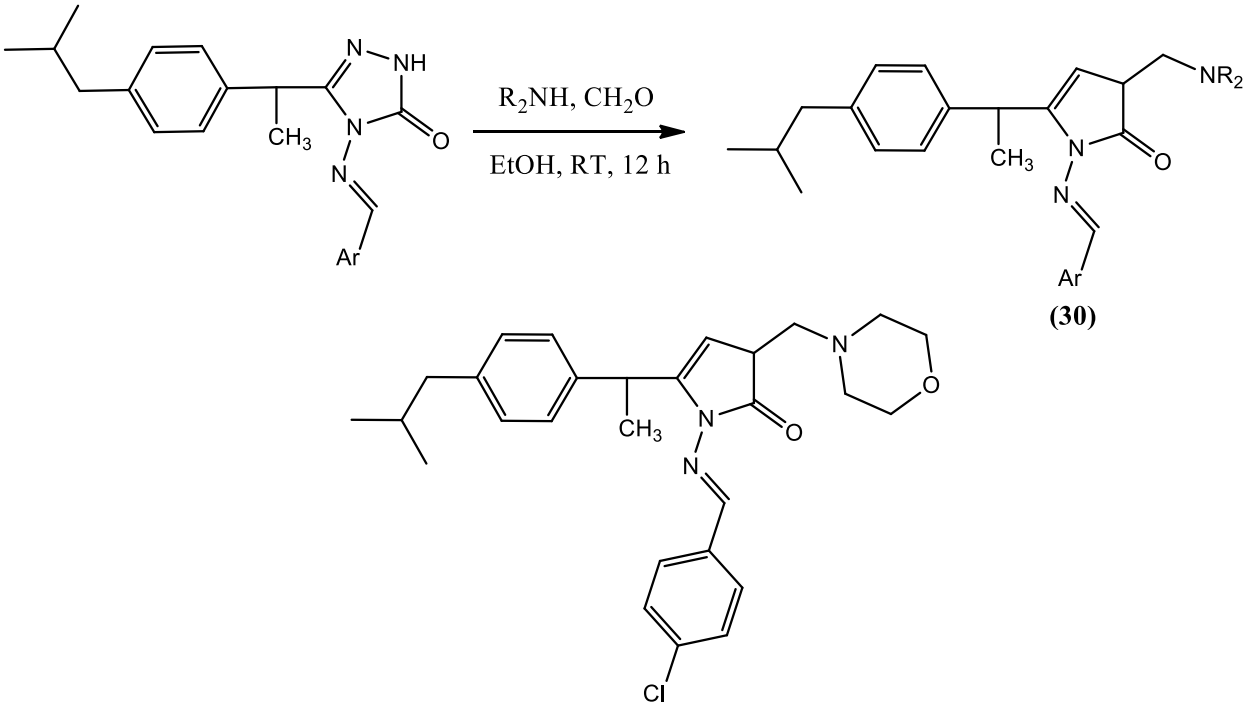
Mycobacterium tuberculosis activity was found in the Mannich product **29**. The corresponding triazole Mannich derivative was obtained from cyclic amines, formaldehyde, and triazole in dioxane- ethanol solvent medium combination (Scheme 10) [244].



Scheme 10. Anti tubercular Mannich Derivatives

3.4.4. Synthesis of Anti-inflammatory Molecules

Pain and inflammation are tested with anti-inflammatory medications. Ibuprofen is well-known non-steroidal anti-inflammatory drug. Which used for a long time may cause ulcers and nephrotoxicity. Non-steroidal anti-inflammatory medication carbonyl derivatives have better anti-inflammatory activity with fewer adverse effects. Newly synthesized ibuprofen triazole Mannich base derivatives **30** prepared from secondary amine with formaldehyde was described by Sujith et al (Scheme 11) [245].



Scheme 11. Ibuprufen Mannich analogues

The ibuprofen Mannich product **31** outperformed the original molecule in terms of anti-inflammatory efficacy. Furthermore, the substance had a strong analgesic impact. Compound **31** had a stronger analgesic impact than diclofenac, the comparative medication.

Chalcone connected heterocyclic Mannich bases (**32a-d**) were obtained via condensation of acetophenone by heterocyclic aldehydes (Fig. 19).

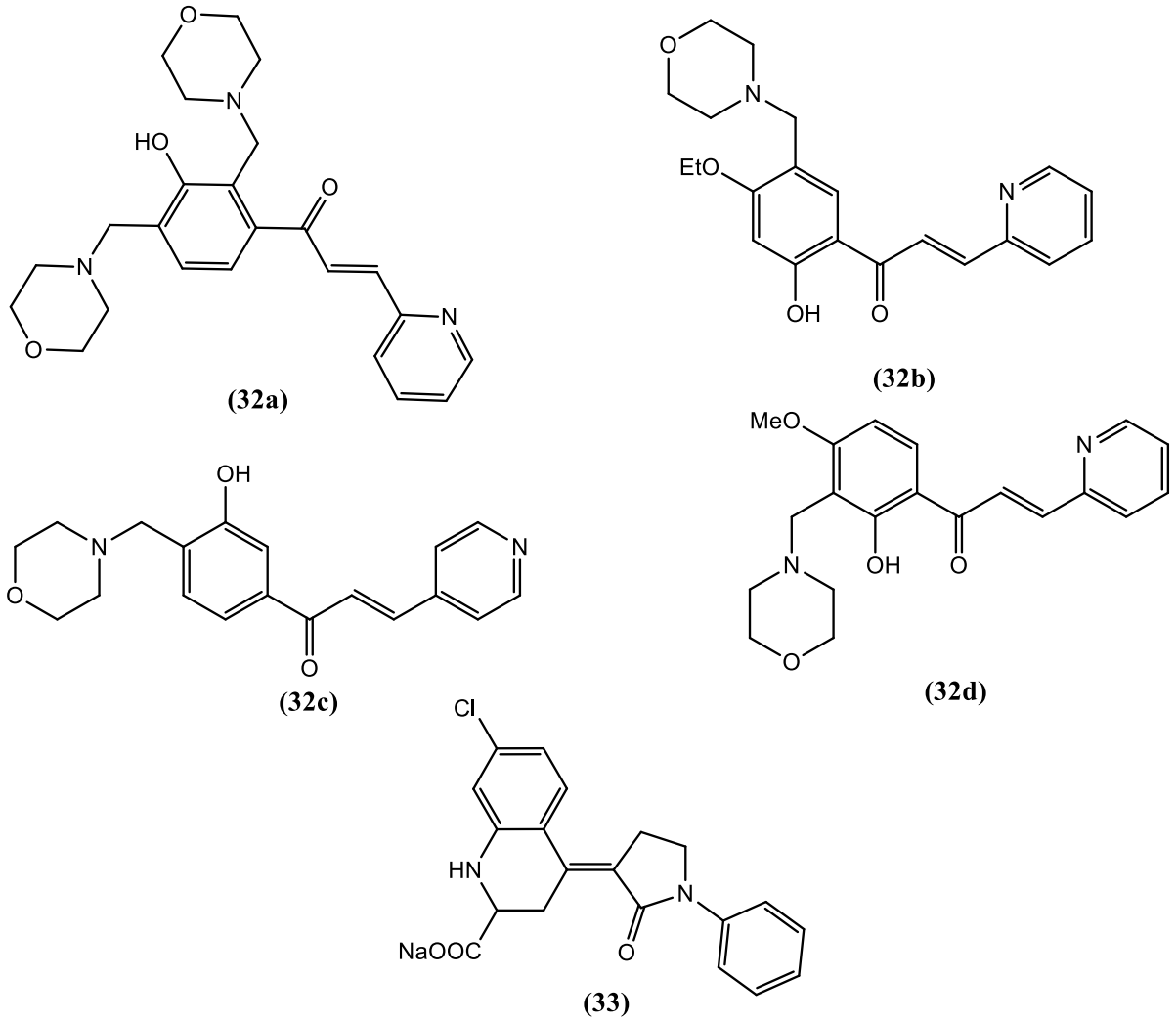


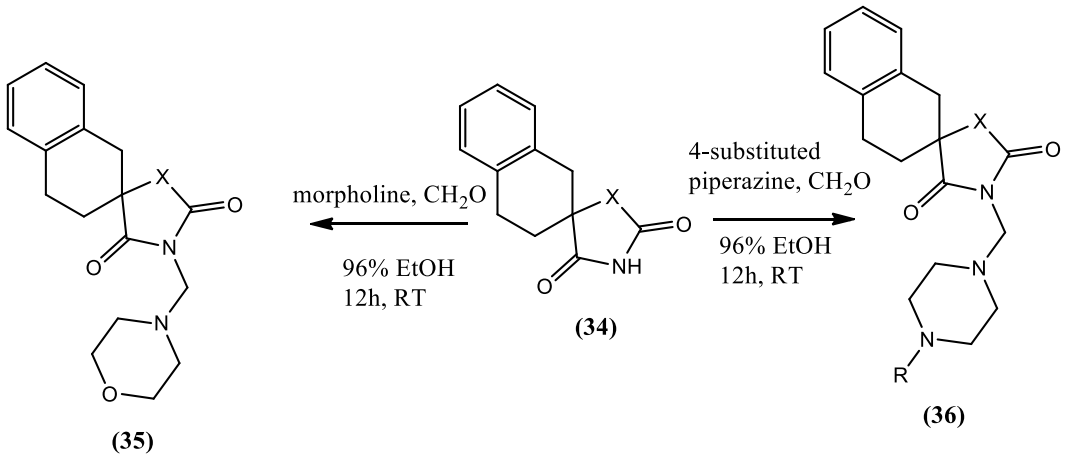
Fig. 19. Anti-inflammatory activity of heterocyclic Mannich base derivatives

The compounds **32a** and **32c** had a strong inhibitory effect on the synthesis of nitric oxide, whereas the mannich base products **32b** and **32d** had a strong inhibitory effect on the production of oxygen (O_2). As a result, Compounds **32a**, **32b** and **32c**, **32d** were may be used as lead compounds in the development of anti-inflammatory medicines. To manufacture orally accessible anti-hyperalgesic tetrahydroquinoline

component **33**, Fabio et al. reported that synthesis of Mannich type condensation reaction by using metal triflate (Fig. 19).

3.4.5. Synthesis of Anticonvulsant activity compounds

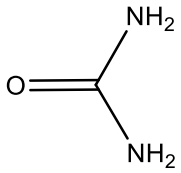
Anticonvulsant active compounds which they are frequently used for the treatment of epilepsy, antiepileptic medicines phenytoin and bipolar disorder, mephobarbital cause drowsiness and hypnosis as adverse effects. New anticonvulsant medicines with low or no adverse effects are sorely needed to manage all types of fits. Obniska et al. recently published a paper on the production and research of mannich base compound **34** obtained from it (Scheme 12). In moderate to excellent yields, (di) azaspirodiones of mannich base derivatives prepared from formaldehyde and substituted piperazine / morpholine produced the respective Mannich base derivatives **35** and **36**. The Mannich compounds outperform the reference medication, phenytoin, in terms of action.



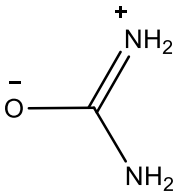
Scheme 12. Synthesis of anticonvulsant active compounds

3.5. General review of urea and Substituted urea connected metal complexes

Due to their fastcoordinating tendencies, diamide, urea, and equivalents, as well as related compounds like thiourea and variants, have been widely studied [246-253]. These ligands have distinct coordination tendencies [254,255]. The canonical forms of urea **37**, **38**, and **39** which these resonance hybrid [256] with approximately 30% contribution from each of the polar formations below.



(37)



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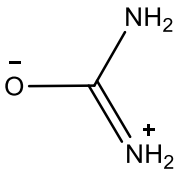


(39)

The allocations for different key bands were reported in literature [257] after a standard co-ordinate examination of urea was performed. In urea the carbonyl stretching was observed at lower frequency compared to in ketones because of the contribution of dipolar resonance forms involved to the structure. NH_2 functional group combined with the carbonyl group in bending modes. So, it's clearly showed is not pure.

If carbonyl oxygen is used for coordination, the polar forms' contribution becomes more significant, and V(c=o) is anticipated to drop and V(c=o) to rise (C-N). However, if the polar structure is used to coordinate the nitrogen atom to the central metal, a higher electron density on the nitrogen atom is anticipated, and

contribution of polar structure was less. As a result, V(c=o) frequency ranges increases in it and a reduction occurred in V(c-N), and frequency ranges decrease in V(c-N) would indicate nitrogen coordination of urea (N-H). While the nitrogen atom is not coordinating, the (N-H) stretching frequency in complexes will occasionally vary. The anions of metal salts are contact with Hydrogen bonding to blame for this.

Analytical and physical methods have been used to study various kinds of urea related metal complexes such as N-alkyl and N-aryl substituted urea derivatives.

Magnetic moments and IR spectra were used to analyze many cobalt (II), manganese (II), and nickel (II) complexes connected with urea [258]. Hexa bis(urea) cobalt (II) sulphato complex was synthesized and studied [259]. IR investigation of oxygen linked Iron (II) and Iron (III) urea complexes and also cadmium (II), zinc (II), and manganese (II) acetate related urea complexes [260] have been studied.

Penland and his colleagues [246] used infrared spectral information to predict the metal-oxygen bond in [Cr.6L] Cl_3 metal complexes, [Zn.2L] Cl_2 and [Fe.4L] Cl_3, (L=urea), whereas V(c=o) frequency ranges decreased from 1683 cm^{-1} to 1505 cm^{-1} was found.

Tetragonal and isomorphous urea metal complexes [261] such as $M(O_2CH)_2.2L$ (M=Mn", Fe", Cd", Ni", Zn") have been discovered. Magnetic susceptibilities of metal complexes like Nickel (II), Iron (II), and Cobalt (II) have

been measured. ML_2Cl_3 (M= Rh III; Ru III; L=urea) and [Pt.4L] Cl_4 with Ruthenium (III), Rhodium (III), and Platinum (IV) chlorides of diamagnetic octahedral complexes have been described [262].

The FT-IR spectrum showed that urea range in the stannic halide complexes were 4000-700 cm^{-1} investigated by Aggarwal and Singh [263], who ascribed the Metal-Oxygen bond based on the carbonyl frequencies. Urea stannous chloride complexes like [$SnCl_2$.L], [$SnCl_2$.2L] and [$2SnCl_2$.L] which have been synthesized and characterized as M-O bound parts.

Various metal salts have been revealed to form aryl altered urea complexes. The complexes [264] formed by N-phenyl urea are $[MU]X_2$ (X = Cl-, Br-, I-; M=Mn", Co";) and $[ML_2X_2]$ (M= Ni", Cu", Co", Zn"). In most of these metal complexes shown that carbonyl oxygen coordination frequency ranges decreased at -1670 cm^{-1} on amide bond I.

Numerous transition metals were shown to form N, N/N, N'-dimethylurea complexes at different stoichiometries. N, N'-dimethylurea connected with Perchlorate complexes has isolated and described the metal complexes whereas [ML6] $(ClO_4)_2$ (M=Mn", Co", Cu") and $[CuL_4(ClO_4)_2]$, as well as Cu" salts taken as 1:2 ratio. MnL_6X_2 (X=I-, ClO_4) and MnL6 $(NCS)_2$ are octahedral complexes formed by the same ligand and Manganese (II) salts [265,266]. When N, N'-dimethylurea combined with manganese (ll) halides to formed the complexes general type

Mn.3L.X_2 (X = Cl-, Br-, I-), and 5-coordinated high spin species identified in the complex Mn.3L.X2 (X = I-, Cl-, Br-,). Nickel (II) and cobalt (II) octahedral and mixed octahedral-tetrahedral geometry [267,268] complexes are formed as [ML_6] [MX_4] (M=Ni"; X=Cl^-, Br^- and M = Co"; X = Cl^-, Br-, NCS^-) and [M.6L.X_2] (M=Ni", Co"; (X =ClO_4^-, Br^-, Cl^-, and I^-) [$NiL_4(NCS)_2$]

To characterize mixed complexes of the type [LnL_3L'Cl] $Cl_2.4H_2O$ L=N-phenylthiourea, L'=urea; (Lni" = Yb, La, Pr, Nd, Sm, Gd, Dy) N, N'-diphenyl thiourea [269] with the help of TG and DTA, electronic spectra, vibrational-rotational spectra, conductivity measurements. Lattice H_2O contains as water molecules. The IR spectra clearly indicated that the oxygen and sulphur are connected with the ligands L and L' correspondingly.

M-O bound moieties found in N-methylurea complexes have already been isolated and which the complexes containing copper (II), manganese (II), iron (II), chromium (II), cobalt (II), nickel (II), zinc (II) [270-274].

The kind of complexes such as [$CoLX_2$] (X = Cl-, Br-, I-) and [CoL_2X_2] are formed by combining polymethylene-1-(phenylthiourea)n-phenylurea, which containing cobalt (II) halides with urea and thiourea units. Only S coordination has been found in [CoL_2X_2], while both S and N and O or S kinds of coordination have been suggested in the [$CoLX_2$] complex [273].

The different type of Copper (II) complexes like [Cu (Pu)nX_2] (X=ClO^{4-}; and BF^{4-}; n=5, 6 and Pu=N, N'-propyleneurea) [Cu (Eu)nX_2] (n=4,5; Eu=N, N'-ethylene urea) have been synthesized by Kovacik and colleagues [274]. Chemical analyses, ligand-field spectra, and ESR spectra were used to investigate the complexes. Copper (II) ion couples with oxygen donor atoms in all molecules.

Numerous tetrasubstituted urea metal complexes containing various metal salts were isolated and its characteristics studied [275-282]. Complexes of the type [Ln.6L] $(ClO_4)_3$ are formed when tetramethylurea is combined with lanthanon perchlorates. When complexed with metals like cobalt (II), copper (II), and iron (II), tetraoxalylurea acts as a polydentate ligand [283]. Tetramethylurea, N, N-dimethyl-N', N'-diphenylurea, N, N-dimethyl-N', N'-diethylurea, and tetraethylurea are some of the tetrasubstituted ureas investigated [284]. With tetrachloro(halosulphato) antimony (IV), tetra methyl urea produces a 1:1 adduct. Antimony is hexacoordinated and the halo sulphate group serves as a monodentate ligand. Tetramethylurea binds with antimony via the nitrogen atom present on it, resulting in the adduct [$SbCl_4(SO_3X)$ (tmu)] (X= Cl^-, F^-). Tetrasubstituted urea Complexes containing cobalt (II), antimony (IV), chromium (III), aluminum (III), vanadlum (IV), antimony (III), tantalum (V), bismuth (III), uranium (IV), thorium (IV), and niobium (V) have all been prepared and characterized as (M-O) bound species [285-290].

Srivatsava and Madhok produced numerous [MoO_2.2L] Cl_2 molybdenum complexes using pyridylurea, RNHCONHR' (R=pyridyl and its substitution; R'=Ortho and Para- tolyl, phenyl), wherein the metal was synchronized to the ligands via heterocyclic ring and carbonyl oxygen [291]. Venkatesa Prabhu et al. reported that synthesis of novel aminobenzylated Mannich bases, piperidinobenzylurea and N, N'-bis(morpholinobenzyl) urea were characterized from using FT-IR, mass spectroscopy, and ^{1}H, ^{13}C- NMR. Piperidinobenzylurea related complex with arrangements [MX_2.2L] and [MX_2. L. nH_2O] (X=Cl^-, Br^-, NO^{3-}; M= Co'', Ni'', and Cu'', Mn II; n=0, 2) has described [291]. The bidendate ligand bonding through carbonyl oxygen atoms and piperidyl nitrogen was shown by IR and ^{1}H NMR spectral information.

Several cyclic urea metal complexes, including such ethyleneurea and propyleneurea, were identified and recognized as metal-oxygen bonding molecules. Ethyleneurea complexes coordinated with metal such as Chromium (III), vanadate (IV), and copper (II), as well as propyleneurea lanthanide complexes, were documented [257]. M-O bonded moieties have been discovered in tetrahedral cobalt (II) complexes containing N,N'-dimethylethyleneurea and N,N'-dimethylpropyleneurea [292-295].

Barbier and Hugel [296] identified complexes with the formulas [Mn.2LX_2] and [Mn.6L]X_2 (X=Br^-, I^-, ClO^{4-}), (X=Cl^-, Br^-), [MnL_6]X_2 and [Mn.4L.X_2] (X=Br^-,

I^-; L=urea) and characterized by using FT-IR spectra which gives the information about the oxygen atom attached kinds whereas magnetic data and electronic spectra display them to devise high spin octahedral geometry.

A molecular and crystal structural analysis of the monoureacopper (II) bromate complex revealed intramolecular and intermolecular hydrogen bonding interactions, and also urea attaching to the metal atom through oxygen [297]. In the solid complex with octahedral geometry, a comparable research on urea connected nickel (II) iodo complex revealed that Ni-I bonds, Ni-O, as well as NH... O, NH... N and hydrogen bonds present in it.

Ramachandra Rao [298] has created a $GdL_5L'_3].3H_2O$ (L1=thiourea, L=urea) mixed complex and IR spectra, TG, and DTA were investigated. By ligand replacement, $[CuLCl_2]$ and $AgLNO_3$ (L=urea) interact with anhydrous liq.NH_3 to produce the respective amine complexes such as M [Ag (SCN)(SeCN)] (L=urea; M= Cu", Co", Ni") bimetallic complexes correspondingly discovered [299].

Only two bands are seen in the diffuse spectral data [300] of the urea complex containing cobalt (II) sulphate. Bennett Larry [301] has created a $[CoL_4(NO_3)_2]$ (L=urea) M-O linked complex. The ligand exhibits unidentate and bidentate behavior in the same complex, according to the IR research. There are additional information findings on M-O bonding in the urea complexes [Cr2LX_2],

[$Cr.4L.X_2$], (X= Cl, Br"; L=urea), [$M(NCS)_2.2L$] (M=Zn", Cd") and [$MCl_4.L$] (M=Tiiv, HfIv, ZrIv) [302].

[Zn (H_2O)$2L_2$]($C1O_4$)$_2$, [ZnL_6] ($C1O_4$)$_2$, and [$Zn(C1O_4)_2.4L$] zinc(II) $2H_2O$ (L=urea) complexes IR research [303] was used to produce and characterize. The coordination of [PtL_2Cl_2] and [PdL_2Cl_2] via the N atom of urea has been described [304]. Singh and Pande [305] identified M-O linked compounds in N-allylurea and acetylene urea complexes and the types were [$MX_4.L$] and [$MX_4.2L$] identified by IR spectrum analysis.

In the instance of lanthanide complexes like N-N'-diethylurea and N, N'-dimethylurea which they have nearly identical coordination propensity. They produce [ML_8]X_3 complexes with 8-fold coordination [306-307] (X=Cl^-, NO_3^-, NCS^-, ClO_4^-; MIII = La-Lu). Metal-oxygen bound species have been identified in N, N'-diethyl urea complexes containing manganese (II), cobalt (II), nickel (II), and lanthanides metals [308-310].

With N, N or N, O donor atoms, Amidinourea displays bidentate behavior. N-benzoylformidino-N-arylcarbamides and thiocarbamides) as well as N,N'-diarylformamidino-n-arylcarbamides and thiocarbamides, produce the octahedral geometry of molybdenum (V) metal complexes with the formula [MoL_2Cl_2]Cl_3, wherein S, O, and N atoms coordinated to the central metal atom. Mercury (II),

niobium (V), and copper (II) metal complexes of similar kinds have been produced and studied [312-314].

Novel oxovanadium (IV), thorium (IV), and Dioxouranium (VI) complexes containing (MBU) N,N'-bis(N-morpholinobenzyl) urea and N-(l-piperidinobenzyl)urea (PBU) were synthesized. The metal complexes were characterized by using elemental analysis, molar conductance, magnetic susceptibility, IR, ^{1}H, ^{13}C-NMR, and thermal investigations [315]. In metal complex ligands are O and N donors based on their IR and 1H NMR spectrum data. PBU coordinates via oxygen atom of urea and the nitrogen present in the piperidine ring, whereas MBU coordinates two morpholine rings through the nitrogen atoms and the oxygen present in urea moiety as a tridentate ligand.

MBU metal complexes (M=Hg", Pb", Sn", and Zn") were synthesized and evaluated [316]. From the result of IR spectra, the frequency ranges of V(C-N-C) V(N-H) and V(C=O), and have been ascribed to the ligands occurred at 1100 cm^{-1} ,3338, and 1627 respectively. The V(C-N-C) and V(N-H) region show a significant negative shift having modest intensity in all of the complexes, suggesting coordination via the urea moieties and the two morpholine moieties' nitrogen. All of the complexes' IR spectra clearly demonstration no change in the V(C-O-C) and V(C=O) and bands location, which indicating that carbonyl oxygen and morpholine oxygen are not involved.

N-(l-piperidinomethyl)urea and N-(l-morpholinomethyl)urea metal complexes were synthesized and spectrally characterized [317,318].

Manganese (II) and Copper (II) connected urea complexes were synthesized and characterized using spectrophotometric approaches. The free urea's FT-IR spectra was matched to that of metal complexes [319]. In manganese (II) compounds, coordination occurs via the oxygen atom, while in copper (II) compounds, coordination occurs over nitrogen and also the oxygen atom.

Infrared spectroscopy [320] was used to synthesize and characterize them, revealing that oxygen bound molecules present in this type of $[Cu_2(O_2CC_5H_{11})_4(urea)]$ and $[Cu_2(O_2CC_nH_{2n+1})_4(urea)]$ (n=5 to 11) metal complexes.

The urea complex of copper such as $[Cu(urea)_4]\ Cl_2$ [321] was already synthesized, and the structure has been determined by EPR, elemental analysis, AAS, and FT-IR. The weight loss of various mediates occurs in four different phases, compared to three different endothermic impacts, according to TGA and DTA analyses. Up to 428 K, the compound is thermally stable.

3.6. General investigation of semi- and thiosemicarbazide derivatives of metal complexes

Thiosemicarbazones and Semicarbazones which are chemical substances with a wide range of applications. For several years, semi- and thiosemicarbazone metal complexes have piqued the attention of numerous researchers. The evidence comes from a large number of articles and reviews [322-330].

Semi- and thiosemicarbazones are represented structurally as follows:

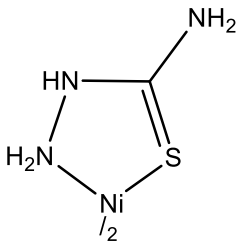
Because of their fast complexation propensity, existence of the coordination chemistry of semi- and thiosemicarbazones, stabilization of different oxidation states of the metals, and a lot of donor atoms seems to be highly intriguing [331,332]. These chemicals may act as a deprotonated ligand or as a neutral ligand. Semicarbazones usually respond in the keto form, however they have recently been found to coordinate in the enol form following deprotonation [333,334].

Because of their application as stabilizers, insecticides, physiologically active chemicals, and analytical reagents, semicarbazones and thiosemicarbazones metal complexes is gaining popularity. The biological activities of semi and thiosemicarbazone complexes vary from that of the ligand or the metal ion

themselves, with enhanced or reduced bioactivities observed in copper (II), iron (II), and zinc (II) metal complexes [335-337].

Jensen [338-340] showed that thiosemicarbazide may build complexes with other transition metal ions. A square planar arrangement produces two kinds of metal complexes [318]. The neutral and ionic metal complexes, with formulas $[M(tsc)_2]$, and $[M(Htsc)_2]^{2+}$ are alluded to as $[M(Htsc)_2]^{2+}$ and $[M(tsc)_2]$, accordingly. A hydrogen atom is removed from thiosemicarbazide in the later compound, enabling it to function as an uninegative ligand [341].

The structure of green colored [Ni(Htsc)2]S04.3H20 was determined using X-rays, and has a square planar trans structure, as illustrated below [342], with coordination happening between the nitrogen of terminal hydrazine and the sulphur atom.



The ligand thiosemicarbazide (Htsc) has been investigated in square planar platinum (II), nickel (II) and palladium (II) metal complexes. For complexes through the general formula $[M(Htsc)_2]^{2+}$, simultaneous cis and trans geometrical isomers are formed, whereas neutral species produced only from the trans isomer. The

stereochemistry given [341] is supported by the infrared and diffuse spectral analysis of these compounds.

The biological actions of thiosemicarbazones, such as anticancer, antibacterial, antiviral, and antimalarial activity, are of great interest [342-352]. When its biological functions are complexed, they become more active. West et al [324,325] investigated the connection between both the structure and bioactivity of semi- and thiosemicarbazones and associated metal complexes.

Thiosemicarbazones have a variety of biological characteristics that are dependent on the parent ketone or aldehyde [353]. Whether these metal complexes are heterocyclic aromatic systems, and the nature of the system appears to increase the biological activity [354-359]. Monica Baldini et colleagues [360] explored copper (ll) complexes containing heterocyclic substituted thiosemicarbazone. 5-Formyluracil thiosemicarbazone as well as its metal complexes have been shown to have much higher biological activity than the free ligand [360]. Copper complexes have better activity than cobalt or nickel counterparts, in addition one of the metal complexes may also cause apoptosis [361,362]. Thiosemicarbazones and related metal complexes have been shown to have antifungal and antibacterial properties [363,364]. Bauer [365] has examined the antiviral activity of thiosemicarbazone. Certain thiosemicarbazones complexes also evaluated for their coordinating characteristics [366-369]. Metal complexes of thiosemicarbazone (M=copper and

zinc) have been shown to be more effective inhibitors of cancer cell proliferation [370].

Numerous copper (II) complexes containing bis(thiosemicarbazone) are being investigated in order to develop a superoxide dismutase (SOD)-like medication capable of crossing the cell membrane and reaching intracellular superoxide producing cells [371,372].

Spectroscopic (IR, ^{1}H NMR) and physical (magnetic moment, conductance) investigations were used to characterize the 5-methylfurfural thiosemicarbazones metal complexes of cadmium (II), nickel (II), copper (II), and cobalt (II) and also these complexes were coordinated by sulphur and azomethine nitrogen, while the coordinated atoms in the cadmium (II) complexes are sulphur and furanic oxygen. In ligand spectra the V(C=N) is attributed to the strong band shown at 1600 cm^{-1}. Except for cadmium complexes, this frequency occurs at higher region in IR spectrum of all the complexes shows that the azomethine group is coordinated through the metal. In the spectra of the complexes, the bands present in the range 3440-3270 cm^{-1}, ascribed to symmetrical and asymmetrical stretching modes $V(NH_2)$ in the ligand spectrum, experience significant modification.

Elemental analysis, TG/DTA, FTIR, and 1H NMR were used to characterize the mono- and bis(thiosemicarbazone) ligands connected with antimony (III) complexes. The coordination of complexes is shown by FTIR spectra to be via

azomethine nitrogen [287]. Utilizing FTIR spectra of complexes, the removal of the V(NH) band owing to deprotonation of all ligands has been demonstrated. The deprotonation of the amino groups during complexation is also seen in ^{1}H NMR studies of complexes.

A novel tridentate ligand with monoxime and thiosemi-carbazone functionalities was produced. Physical and spectroscopic techniques are used to produce and analyze its nickel (II), palladium (II) and copper (II), thiosemicarbazone complexes. The coordination of the imine nitrogen is shown by the change of the imine V(C=N) region of the oxime thiosemicarbazones between the ranges from 1595 cm^{-1} to 1527-1572 cm^{-1} for metal complexes [373].

Anil D Naik et al [369] reported that the synthesis of different type of novel copper (II) binuclear complexes obtained from 4-(X-Phenyl) thiosemicarbazide and 2,6-diformyl-p-cresol (where X= -H, m-CH_3, p-CH_3 and o-CH_3) by using Schiff base method. Metal complex coordination is mediated by sulphur and imine nitrogen, according to its FT-IR spectrum.

N.K. Singh et al [374] investigated a novel possible tetradentate ligand, N'-p-hydroxythiobenzhydrazine, which produces copper (II) and zinc (II) metal complexes. From the ESR spectrum give g values that are typical of square planar, square pyramidal, and octahedral geometry of copper and iron metal complexes. IR, ESR and electronic spectrometry, Molar conductance, magnetic moments were used

to characterize iron (II) copper (II), cobalt (II), and nickel (II) complexes using 1-Phenyl-l,2-propanedione-2-oximethiosemlcarbazone [375]. A prominent band in the PPDOT spectra at 1201 cm^{-1} is moved to a lower region, suggesting that thio keto sulphur is involved in coordination. In addition, the imine band found at 1610 cm^{-1} and moved to a lower range for the PPDOT complexes, indicating that the (C=N) imine nitrogen atom is involved in metal coordination.

N-(l-morpholinobenzyl) semicarbazide connected metals of zinc (II), copper (II), nickel (II), and cobalt (II) complexes were prepared and characterized by using magnetic and spectroscopic investigations by N. Raman et al [376]. The complexes are square-planar in shape. In free ligand V(C=O) region is not seen in the spectra of semicarbazone complexes, suggesting that C=O enolisation proceeded with complexation and deprotonation by metal ions. Nitrogen of azomethine is coordinated to the metal which was indicated from the result of V(C=N) frequency shift to lower wave number. The ligand's 3240 cm^{-1} band is missing in the complexes, indicating that the ligand's -NH is deprotonated previous to coordinated to the metal complex. This result verified by ^{1}H NMR experiments. This experimental data leads to the conclusion that the ligand plays as a monobasic bidentate throughout all complexes. Using X-ray investigations, Jayendra Patole et al [377] produced salicylaldehydesemi- and thiosemicarbazide of copper (II) complexes were studied its structural properties. The semlcarbazone ligand's chloro

compound is monomeric and has a square planar shape, whereas the nitro complex is diametric. Human breast cancer cells were used to test these complexes for anti-proliferative effects.

Salicylaldehyde semicarbazone and thiosemicarbazone ligands [378] have been shown to be helpful in the design of active anti-cancer drugs with antiproliferative properties which can be regulated by the copper (II)/copper (I) redox pair.

Magnetic measurements, electronic absorbance, and IR spectrometry were used to characterize the compound 6-diacetylpyridinebis(semi- and thiosemicarbazones) containing copper (II) complex [379]. The coordination of semi- and thiosemicarbazones is achieved via sulphur and azomethine nitrogen, according to IR spectrum data.

Spectral techniques were used to characterize the isothiosemicarbazones, pyridoxolsemi-, and thiosemi (PLITSC, PLTSC, and PLSC respectively) connected metal complexes [380].

CDOTSC (cis-3,7-dimethyl-2,6-Octadienthiosemicarbazone) [381] transition metal complexes were produced and characterized by using spectral and elemental techniques (IR, electronic, and ^{1}H NMR). [M.2L.Cl_2] type metal complexes which are ligand = CDOTSC; Cd", Co", Cu", Ni", Zn«, and Hg". The ligand roles as a bidentate throughout all complexes. Distorted octahedral geometry has been

suggested for copper (II) complexes, as well as octahedral geometries for all the complexes. The coordinated atoms are the sulphur atom of the C=S group and the azomethine nitrogen (C=N), according to the IR spectra of CDOTSC and that of its metal complexes.

MATERIALS AND METHODS

CHAPTER – IV
MATERIALS AND METHODS

We used the active hydrogen atom and put it through the Mannich process using salicylaldehyde and a few secondary amines. Below is a list of the methods and materials that were employed.

4.1. Chemicals Used

For aminating purposes, we used 1,3-cyclohexanedione as the active hydrogen component, Salicylaldehyde as the selective reactant, and Semicarbazide, Urea, and Thiourea as secondary amine reactants. In all reactions, ethanol is typically utilized as a solvent. Chloroform and Dimethylsulfoxide were also employed for solubility experiments. All of these chemicals were Analar grade (A.R) goods from Sigma-Aldrich, and they were utilized as just that.

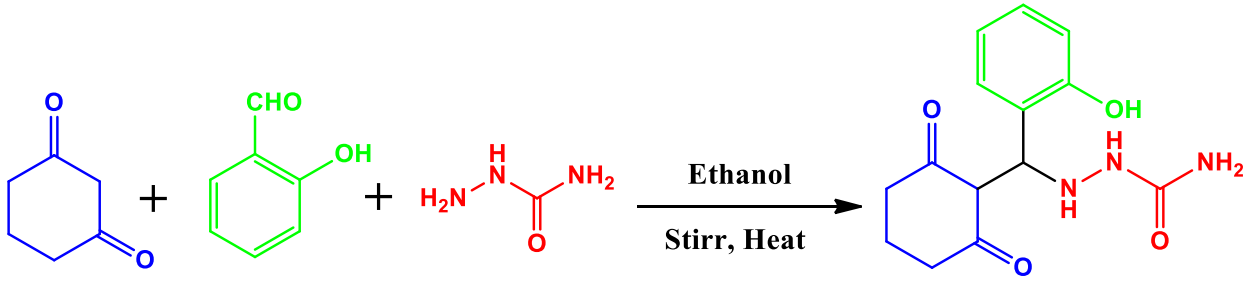
4.2. Synthesis of the Ligands (1-3)

The active hydrogen molecules were condensed using salicylaldehyde and the secondary amine during the ligand production. Three series of synthesis were carried out, with one novel ligand produced in each series, as shown below.

4.2.1. Synthesis of Ligand (1)

In a 100mL RB flask, 1,3-cyclohexanedione (5.60 g, 0.05 mol), salicylaldehyde (6.1 mL, 0.05 mol), and Semicarbazide (0.05 mol, 5.57 g) were

dissolved in 20mL ethanol. The contents of the flask are thoroughly stirred after 30 minutes of heating using a magnetic stirrer. After then, a brilliant crimson residue appeared. It has been dried and filtered. To produce pure product, the final prepared sample was recrystallized in hot ethanol. In Scheme 13, the production of ligand 1 is shown.



Scheme. 13. Synthesis of ligand 1

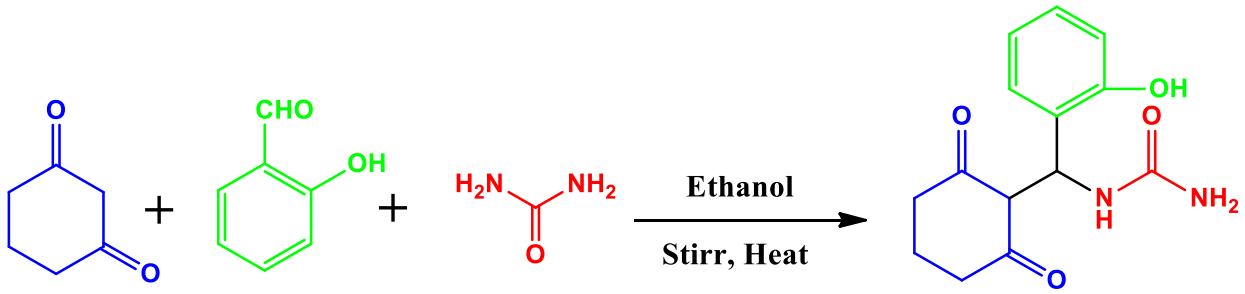
4.2.1.1. 2-((2,6-dioxocyclohexyl)(2-hydroxyphenyl) methyl) hydrazine carboxamide (1)

Red solid; mw: 291.30; mp:184°C; IR (KBr cm^{-1}) ν_{max}: 3435.94 (-OH), 2950.12 (-NH), 1638.73 (-C=O), 1237.44 (-C-N-C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (s, 1H, NH), 7.12-6.90 (m, 4H, Ph-OH), 6.81 (d, *J* = 1.4 Hz ,1H, NH), 6.25 (s, 2H,NH_2), 5.64 (s, 1H, OH), 5.32 (d, *J* = 1.7 Hz, 1H, CH-Ph), 4.34 (d, *J* = 6.9 Hz, 1H, CHD), 2.47-1.95 (m, 6H, CHD); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 208.83 (2C, C=O), 157.43 (1C, C=O), 154.01 (1C, C-OH), 130.19, 128.12, 126.56, 121.18, 115.72 (5C, Ar ring), 69.81 (1C, CH), 45.61 (1C, CH), 40.85 (2C, CH_2), 16.57 (1C, CH_2); EI-MS:

m/z 292.41 (M^+,15%); Elemental analysis: Anal. Calcd. for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42;%. Found: C, 57.70; H, 5.84; N, 14.48;%.

4.2.2. Synthesis of Ligand (2)

In a 100mL RB flask, 1,3-cyclohexanedione (5.60 g, 0.05 mol), salicylaldehyde (6.1 mL, 0.05 mol), and urea (0.05 mol, 3.0 g) were dissolved in 20mL ethanol. The contents of the flask are thoroughly stirred after 30 minutes of heating using a magnetic stirrer. Afterwards, a white dust-like residue developed. It has been dried and filtered. To produce pure product, the final prepared sample was recrystallized in hot ethanol. In Scheme 14, the production of ligand 2 is shown.



Scheme. 14. Synthesis of ligand 2

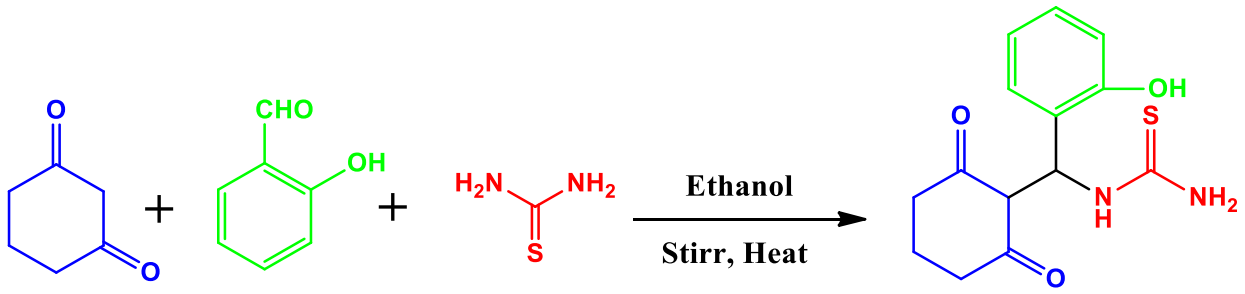
4.2.2.1. 1-((2,6-dioxocyclohexyl)(2-hydroxyphenyl)methyl)urea (2)

Dust white solid; mw: 276.29; mp:146°C; IR (KBr cm^{-1}) ν_{max}: 3436.28 (-OH), 3076.46 (-NH), 2924.22 (-CH), 1641.32 (-C=O), 1236.77 (-C-N-C); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (s, 1H, NH), 7.12-6.90 (m, 4H, Ph-OH), 5.55 (s, 2H,NH_2), 5.32 (d, *J* = 1.7 Hz, 1H, CH-Ph), 5.30 (s, 1H, OH), 4.22 (d, *J* = 6.9 Hz, 1H, CHD),

2.40-1.91 (m, 6H, CHD); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 208.83 (2C, C=O), 162.72 (1C, C=O), 154.0 (1C, C-OH), 130.19, 128.12, 126.50, 121.13, 115.75 (5C, Ar ring), 72.10 (1C, CH), 56.01 (1C, CH), 40.89 (2C, CH_2), 16.57 (1C, CH_2); EI-MS: m/z 277.38 (M^+,16%); Elemental analysis: Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14;%. Found: C, 60.84; H, 5.86; N, 10.12;%.

4.2.3. Synthesis of Ligand (3)

Thiourea (0.05 mol, 3.80 g), 1,3-cyclohexanedione (5.60 g, 0.05 mol), and salicylaldehyde (6.1 mL, 0.05 mol) were diluted in 20 mL ethanol and placed in a 100 mL RB flask. The contents of the flask are thoroughly stirred after 30 minutes of heating using a magnetic stirrer. Afterwards, a white dust-like residue developed. It has been dried and filtered. To produce pure product, the finished prepared sample was recrystallized in hot ethanol. In Scheme 15, the production of ligand 3 is shown.



Scheme. 15. Synthesis of ligand 3

4.2.3.1. 1-((2,6-dioxocyclohexyl)(2-hydroxyphenyl)methyl)thiourea (3)

Yellow solid; mw: 292.35; mp:168°C; IR (KBr cm^{-1}) ν_{max}: 3399.32 (-OH), 3078.08 (-NH), 2925.18 (-CH), 1641.58(-C=O), 1236.48 (-C-N-C); ^1H NMR ($CDCl_3$, 300

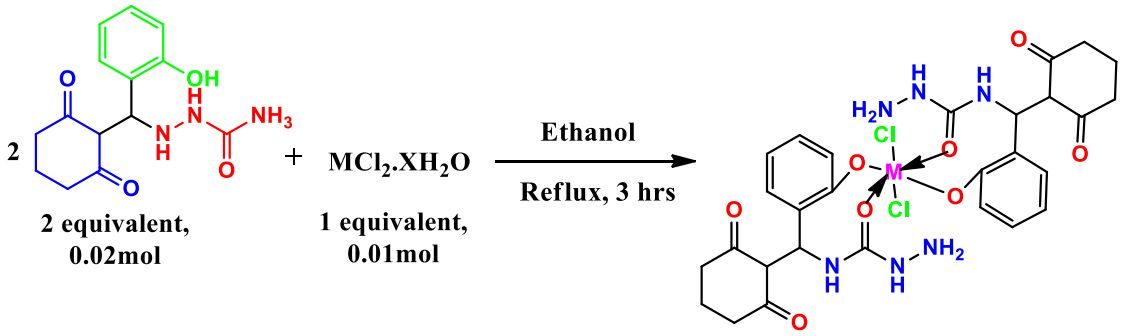
MHz) δ 8.34 (s, 1H, NH), 7.14-6.78 (m, 4H, Ph-OH), 5.64 (s, 2H,NH_2), 5.46 (d,*J* = 1.5 Hz, 1H,CH-Ph), 4.34 (d,*J* = 6.9 Hz, 1H,CHD), 5.30 (s, 1H, OH),2.47-1.85 (m, 6H, CHD); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 208.34 (2C, C=O), 182.01 (1C, C=S), 154.0 (1C, C-OH), 130.92, 128.14, 126.56, 121.18, 115.70 (5C, Ar ring), 72.82 (1C, CH), 61.14 (1C, CH), 40.85 (2C, CH_2), 16.50 (1C, CH_2); EI-MS: m/z 293.48 (M^+,17%); Elemental analysis: Anal. Calcd. for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58;%. Found: C, 57.50; H, 5.54; N, 9.60;%.

4.3. Synthesis of Metal Complexes

Five transition metals, namely copper, nickel, iron, chromium, and manganese, were used to produce complex with ligands (**1-3**). The following procedure was used to carry out the complexation reaction.

4.3.1. Synthesis of metal complexes (1a-1e)

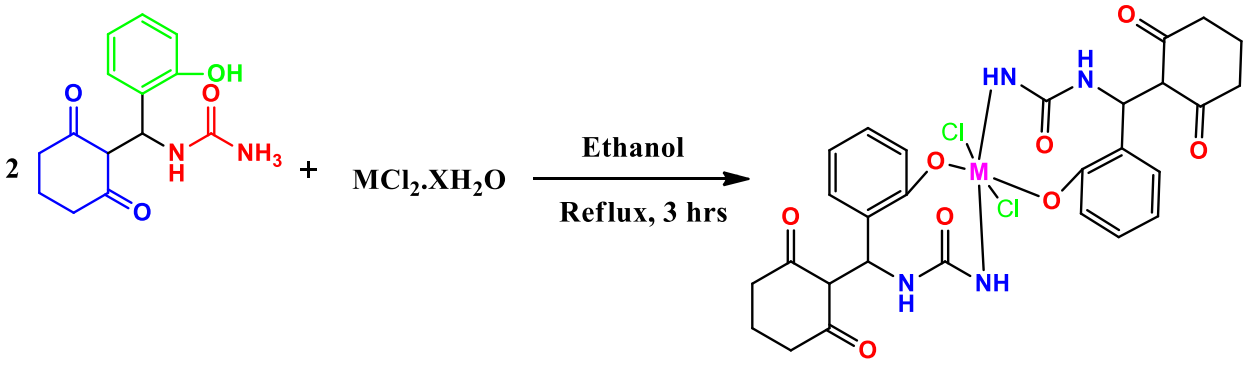
Under continuous stirring, ligand **1** of hot ethanolic solution of (2 equivalent, 0.02 mol) was progressively combined with a metal chlorides in hot ethanolic solution (1 equivalent, 0.01 mol) under reflux. After refluxing for 1-2 hours, the mixture was chilled and stored in the refrigerator for a few hours. In each instance, the colored solid complexes were separated. It was filtered before being rinsed with 50% alcohol and dried.



Scheme. 16. Synthesis of complexes (1a-1e)

4.3.2. Synthesis of metal complexes (2a-2e)

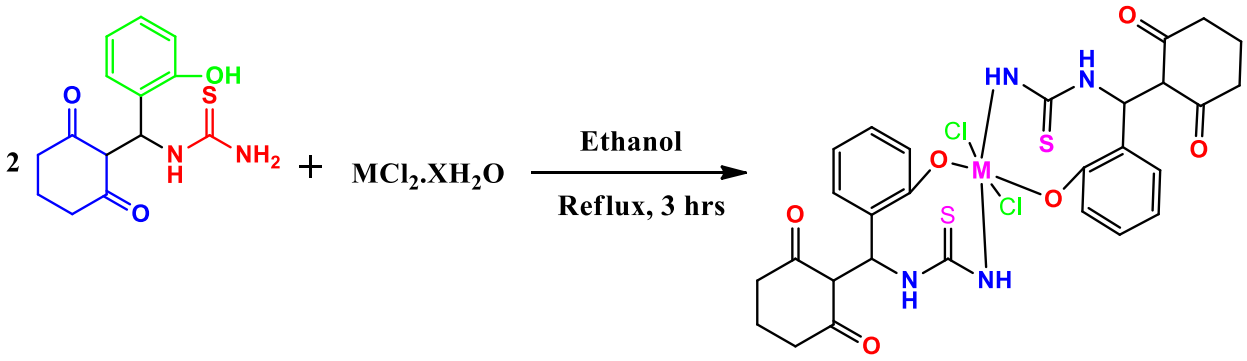
While continuous stirring, a hot ethanolic solution of ligand 2 (2 equivalent, 0.02 mol) was progressively combined with a hot ethanolic solution of metal chloride (1 equivalent, 0.01 mol) over reflux. After refluxing for 1-2 hours, the mixture was chilled and stored in the refrigerator for a few hours. In each instance, the colored solid complexes were separated. It was filtered before being rinsed with 50% alcohol then dried.



Scheme. 17. Synthesis of complexes (2a-2e)

4.3.3. Synthesis of metal complexes (3a-3e)

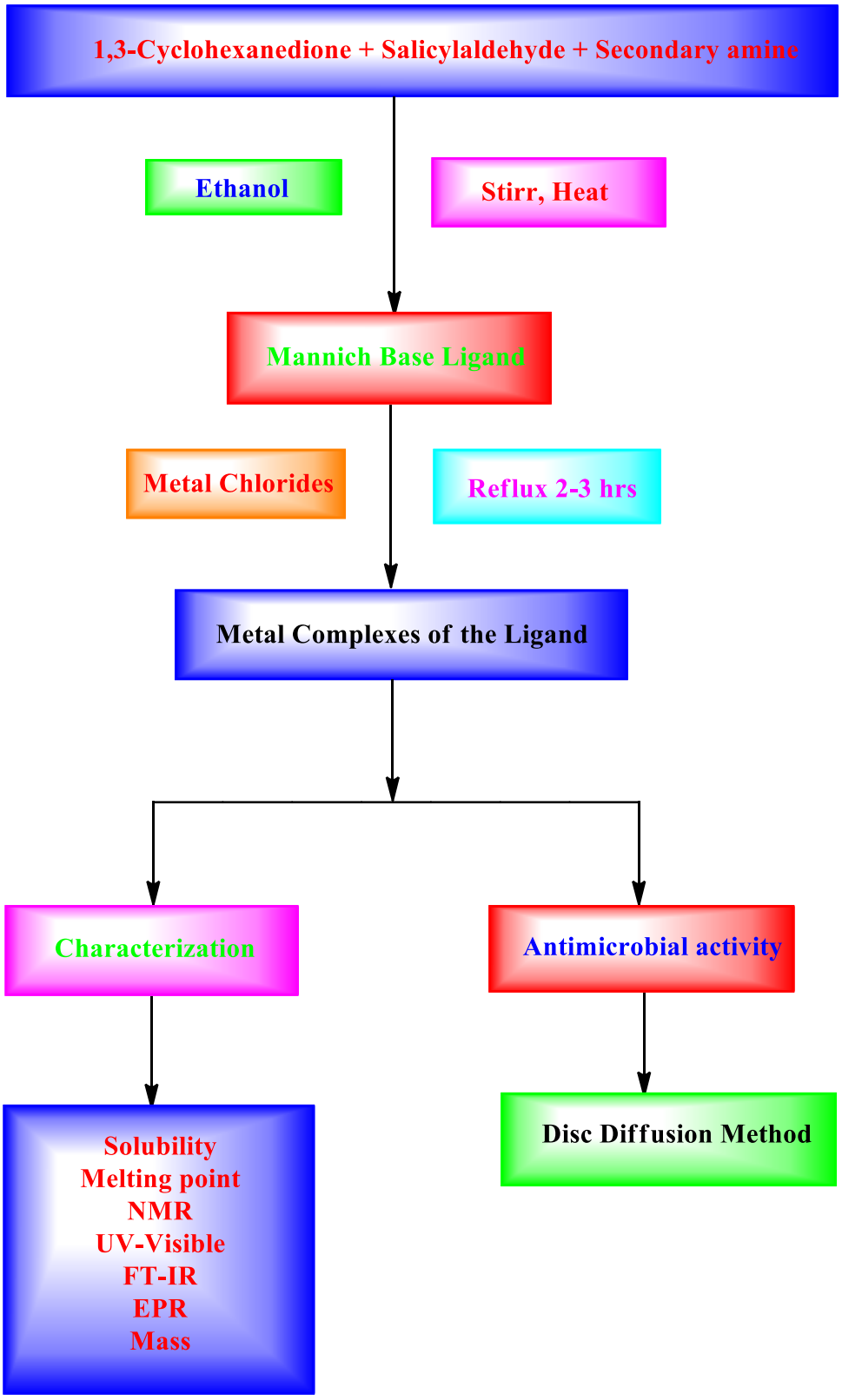
Under continuous stirring, ligand **3** of hot ethanolic solution of (2 equivalent, 0.02 mol) was progressively combined with a metal chlorides in hot ethanolic solution (1 equivalent, 0.01 mol) over reflux. After refluxing for 1-2 hours, the mixture was chilled and stored in the refrigerator for a few hours. For each instance, the colored solid complexes were isolated. It was filtered whilst being rinsed using 50% alcohol then dried.



Scheme. 18. Synthesis of complexes (3a-3e)

4.4. Flow Chart

For a fast overview, the above-mentioned synthetic pathways are shown in the flow chart below.


1,3-Cyclohexanedione + Salicylaldehyde + Secondary amine
Ethanol
Stirr, Heat
Mannich Base Ligand
Metal Chlorides
Reflux 2-3 hrs
Metal Complexes of the Ligand
Characterization
Antimicrobial activity
Solubility
Melting point
NMR
UV-Visible
FT-IR
EPR
Mass
Disc Diffusion Method

4.5. Characterization of the Ligand and the Complexes

The freshly synthesized Mannich base ligands and metal complexes were characterized as follows.

4.5.1. Solubility Measurements

The solubility of the ligand and complexes in protic and aprotic solvents has been determined. Water, ethanol, acetone, chloroform, and dimethylsulfoxide were employed as solvents. Subsequent experiments were planned based on the findings of the solubility tests.

4.5.2. Melting Point

Melting point instrument was used to determine the melting points of the ligands and metal complexes.

4.5.3. Magnetic Susceptibility Measurement

To determine the geometries of the complexes, magnetic susceptibility measurements may be combined with electronic spectra. In the situations of d^5, d^6, d^7, d^8, and d^9 metal ion complexes, tetrahedral, square planar, or octahedral stereochemistries and spin-free or spin-paired character of the complexes may be identified from magnetic criteria. Using a Gouy magnetic balance, magnetic measurements of the present complexes were made to calculate the optimum magnetic moment for each metal atom in the complexes at room temperature. Mercury(II) tetrathiocyanatocobaltate(II), $Hg[Co(SCN)_4]$, was used to calibrate the

Gouy tube. Pascal's constants were used to calculate diamagnetic corrections for different atoms and structural units. Curie's formula, $\mu_{eff} = 2.84 [\chi_M^{corr} T]^{1/2}$ B.M., was used to determine the effective magnetic moments ($\mu_{eff.}$) from the corrected molar magnetic susceptibilities (χ_M^{corr}) of the complexes, where T is the absolute temperature at which the measurements were made. The effective magnetic moment, eff, of the metal ion may be used to calculate the amount of unpaired electrons 'n' it has. The equation $\mu_S = [n (n+2)]^{½}$ gives the contribution to the moment from the electronic spin effect (μ_S).

4.5.4. NMR Spectra

To investigate the structure of the ligands, ^{1}H and ^{13}C NMR spectrum of ligands (**1-3**) remained acquired via a Bruker AMX400 NMR spectroscopy utilizing Chloroform / DMSO solvents in the chemical shift range of 0 ppm to 10 ppm.

4.5.5. FT - IR Spectra

To determine the complexation, the vibrational spectra and FT-IR spectra for the ligands and complexes were obtained through the use of an Agilet Resolutions FT-IR spectroscopy with KBr pellets in the frequency area 400-4000 cm^{-1}.

4.5.6. UV- Visible Spectra

The UV-visible spectra of ligands (**1-3**) and metal complexes (**1a-1e**), (**2a-2e**), (**3a-3e**) were recorded in the range 300-1100 nm using a Shimadzu UV mini-1240 UV spectrophotometer to determine the kinds of electronic transformations that might occur.

4.5.7. Mass Spectra

The mass spectra of ligands (**1-3**) were recorded using an Agilent model 1100 MSD mass spectrophotometer (Minneapolis, MN, USA) to determine the molecular weight and kinds of molecular fragmentations that might occur.

4.6. Antibacterial activity

Antibacterial assessments of the ligands (**1-3**) and its complexes (**1a-1e**), (**2a-2e**), (**3a-3e**) were experienced in vitro against the bacteria *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumaniae*, and *Pseudomonas aeruginosa* by Kirby Bauer Disc diffusion method [382]. The antibacterial activity of ciprofloxacin was utilized as a reference. The bacterial cultures were cultivated on petri dishes on nutrient agar medium. The compounds were synthesized in DMSO and immersed in a 5 mm diameter, 1 mm thick filter paper disc. After 24 hours, the width of the inhibitory zone [383,384] surrounding each disc was evaluated for antibacterial activity, and the discs were put on the already implanted plates and incubated at 37°C. Minimum inhibitory concentrations (MIC) were used to reflect the

antibacterial activity of ligands (**1-3**) and its metal complexes (**1a-1e**), (**2a-2e**), (**3a-3e**).

4.7. Antifungal Activity

The standardised disc–agar diffusion technique [385,386] was used to assess the antifungal activity of ligands (**1-3**) and their complexes (**1a-1e**), (**2a-2e**), and (**3a-3e**). *Microsporum audouinii* (MTCC-8197), *Candia albicans* (MTCC-227), *Cryptococcus neoformans* (recultured) and *Aspergillus niger* (MTCC-872) were used to test antifungal activity. The materials were sterilised by filtering using 0.22 m Millipore filters after being dissolved in 10% dimethyl sulfoxide (DMSO) to a desired concentration of 30 mg/mL. Antifungal studies were then performed utilising disc diffusion technique with 100 litres of solution containing 104 spore/mL of fungi dispersed over PDA medium. The discs (6 mm in diameter) were treated with 10 mL of the samples (300 g/disc) and put on the infected agar. The typical medicine was **amphotericin B**. 10 percent DMSO was used to make negative controls. For fungus specimens, the inoculation plates were then incubated at 37°C for 72 hours. Fungi linked with plants were cultured at 27°C. The zone of inhibition against the tested strains was used to assess antifungal activity. In this study, each test was carried out twice.

RESULTS AND DISCUSSION

CHAPTER – V

RESULTS AND DISCUSSION

To characterize the ligands and complexes created, they were exposed to a variety of physical and spectroscopic techniques. Solubility experiments, melting point assessments, and spectrum techniques such as UV-Visible spectra, ^{1}H & ^{13}C NMR spectra, and FT-IR spectra were also conducted.

The following are the findings of the various physical and spectral techniques for the three distinct classes of ligands and its associated metal complexes, as well as its mosquito larvicidal activity towards *Culex quinquefasciatus* 2nd instar south urban mosquito larvae.

5.1. Metal complexes (1a-1e) with ligand (1)

5.1.1. Physical data

Table 1 shows the physical belongings of the complexes (**1a-1e**) generated from ligand (**1**).

Table 1. Physical data of the complexes (1a-1e) and ligand (1)

Compound	Colour	Melting point (°C)
Ligand (1)	**Red**	**184**
Copper complex (1a)	**Blue**	**210**
Nickel complex (1b)	**Pale green**	**214**
Iron complex (1c)	**Brown**	**226**
Chromium complex (1d)	**Green**	**208**
Manganese complex (1e)	**White**	**220**

5.1.2. Solubility

The solubility of the ligand (**1**) and its associated complexes (**1a-1e**) in various solvents was investigated, and the findings are shown in Table 2. The ligand (**1**) as well as the metal complexes (**1a-1e**) soluble more readily in aprotic solvents than in protic solvents, according to solubility experiments.

Table 2. Solubility test results complexes (1a-1e) and ligand (1)

Compound	Water	Ethanol	Chloroform	DMSO
Ligand (1)	Insoluble	Insoluble	Sparingly soluble	Soluble
Copper complex (1a)	Insoluble	Insoluble	Insoluble	Soluble
Nickel complex (1b)	Insoluble	Insoluble	Insoluble	Soluble
Iron complex (1c)	Insoluble	Insoluble	Insoluble	Soluble
Chromium complex (1d)	Insoluble	Insoluble	Insoluble	Soluble
Manganese complex (1e)	Insoluble	Insoluble	Insoluble	Soluble

5.1.3. Conductivity and magnetic susceptibility measurements

Numerous solvents, including water, ethanol, chloroform, and DMSO, were used to test the solubility of the newly synthesized metal complexes. The Equiptronics digital conductivity meter (Model EQ-660) was used to determine molar conductance in DMSO, with the cell constant calibrated using 0.1M KCl solution. The electrical conductivity of a 10^{-3} M solution of respective complexes in DMSO were determined, revealing the complexes' neutral (non-electrolytic) character. The molar conductance of the mixed ligand complexes (**1a-1e**) of ligand

(**1**) ranges from 18 to 28 $\Omega^{-1}mol^{-1}cm^2$. The chloride ions were shown to be coupled to metal ions via conductivity tests, suggesting that they function as ligands rather than ions. Components for the produced complexes were selected depending on the metal – ligand ratios (1:2) and the type of the electrolytes as determined by conductance experiments, which aids in determining the structure of the complexes. The conductance and magnetic properties of metal complexes (**1a-1e**) with ligand (**1**) were shown in Table 3.

Table 3. Conductance and magnetic properties of metal complexes (1a-1e) with ligand (1)

S. No	Compounds	Conductance ($\Omega^{-1}mol^{-1}cm^2$)	Magnetic Susceptibility (μ_{eff}. B.M)
1.	Copper complex (1a)	18	2.23
2.	Nickel complex (1b)	28	3.70
3.	Iron complex (1c)	24	5.62
4.	Chromium complex (1d)	22	4.80
5.	Manganese complex (1e)	23	5.32

5.1.4. NMR Spectral studies of ligand (1)

The hydrogens of the aromatic rings show a multiplet at 7.12-6.90 ppm in the ^{1}H NMR spectrum of the Mannich base ligand (**1**) below investigation (Fig. 20). The methylene hydrogens linked to the salicylaldehyde and amine hydrogens of the semicarbazide show as a peak at 4.34 ppm, whereas the aromatic –OH occurs at 5.64 ppm. The absence of an indication equivalent to the secondary amine $–NH_2$ proton as it was removed in the Mannich process further confirms the creation of the ligand. The carbons of the aromatic rings had peaks at 130.19-115.72 ppm in the ^{13}C NMR spectra of the Mannich base ligand (**1**) under investigation (Fig. 21). The presence of a peak at 45.61 ppm shows that the methylene carbon is linked to the semicarbazide's salicylaldehyde and amine hydrogens, respectively. Furthermore, the carbonyl carbons of the 1,3-cyclohexanedione and semicarbazide moiety are represented by the peaks at 208.83 and 157.43 ppm, accordingly.

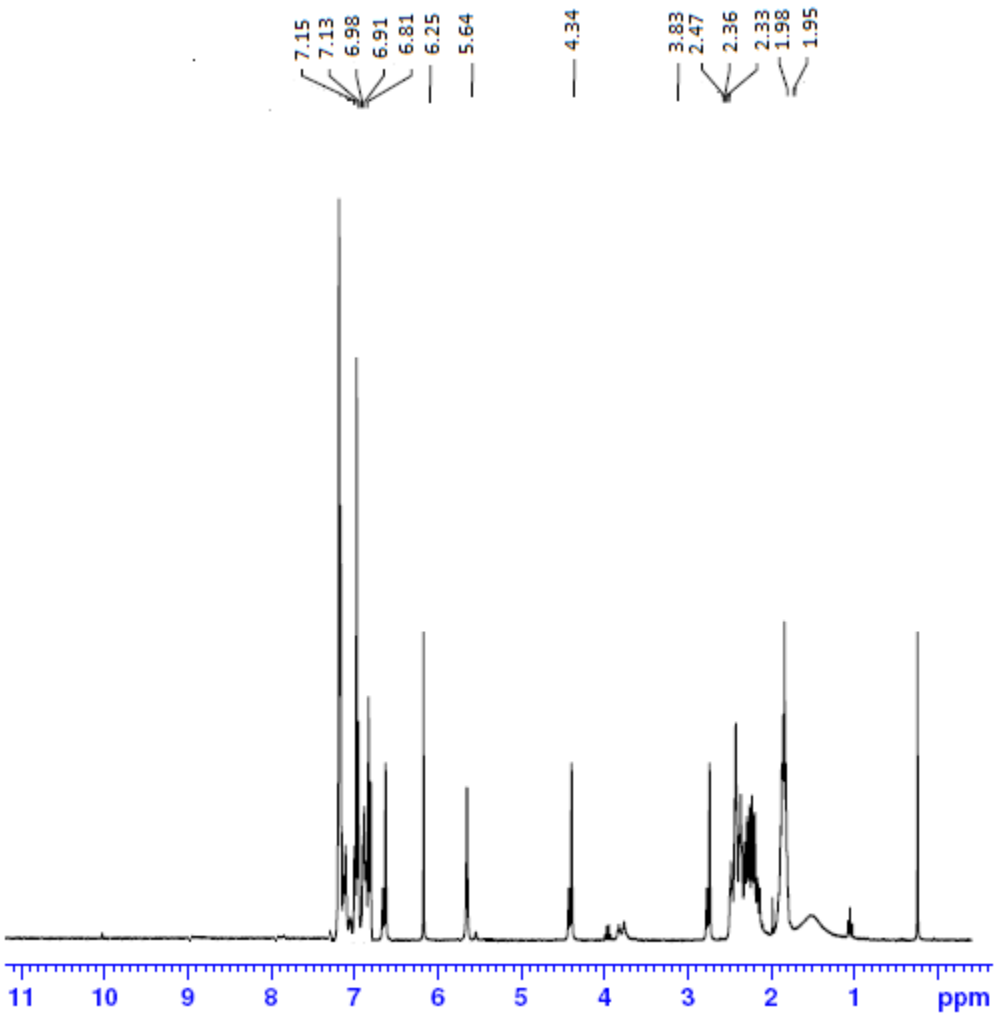


Fig. 20. Ligand (1)-^{1}H-NMR spectra

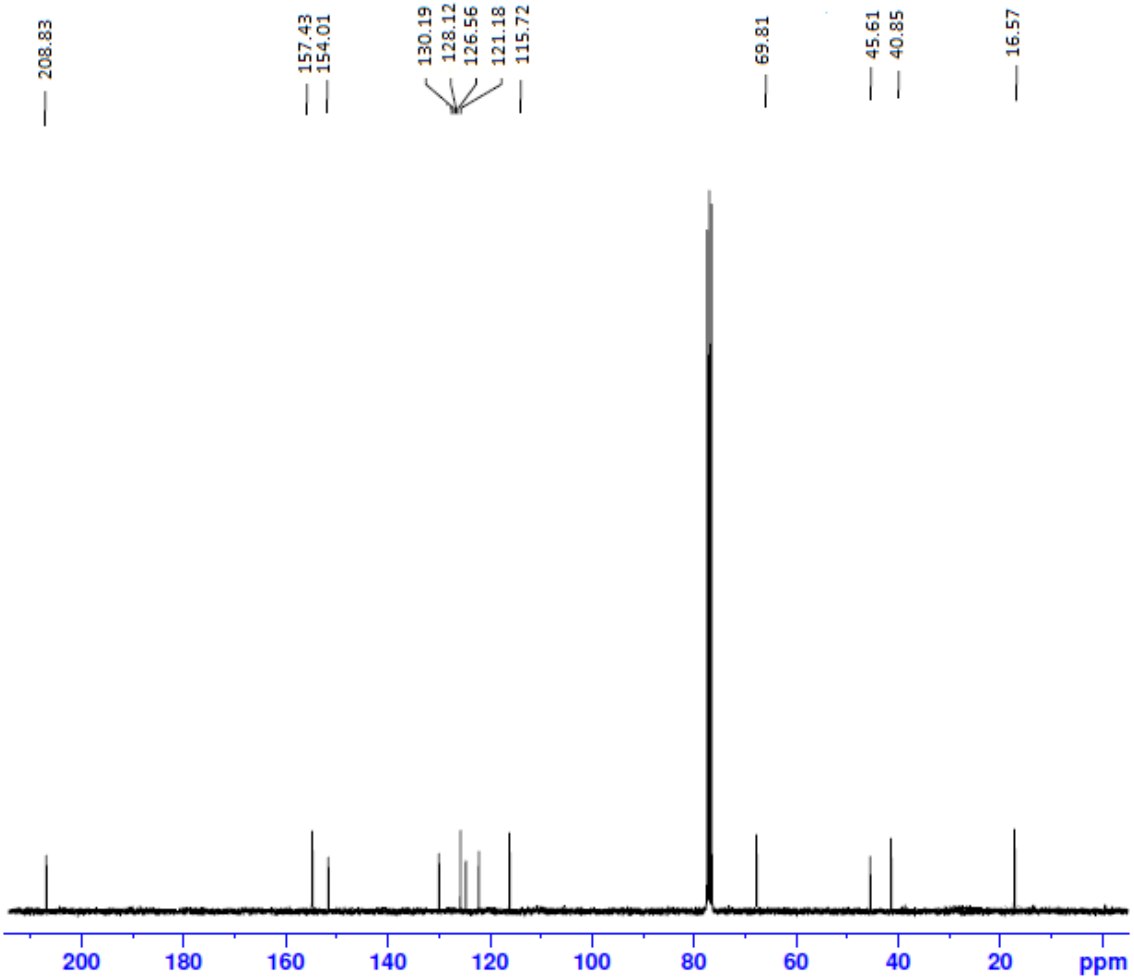


Fig. 21. Ligand (1)-^{13}C-NMR spectra

5.1.5. Mass Spectral studies of ligand (1)

The mass spectrum of the Mannich base ligand (**1**) below investigation (Fig. 22). The observed molecular weight of ligand (**1**) is 291.30 and that was confirmed by mass spectrl studies at m/z 292.41. The molecular ion peak appeared at m/z 120.71. The other fragmentation peasks were m/z 281.83, 258.78, 207.32, 146.89, 72.70 and 42.67 respectively.

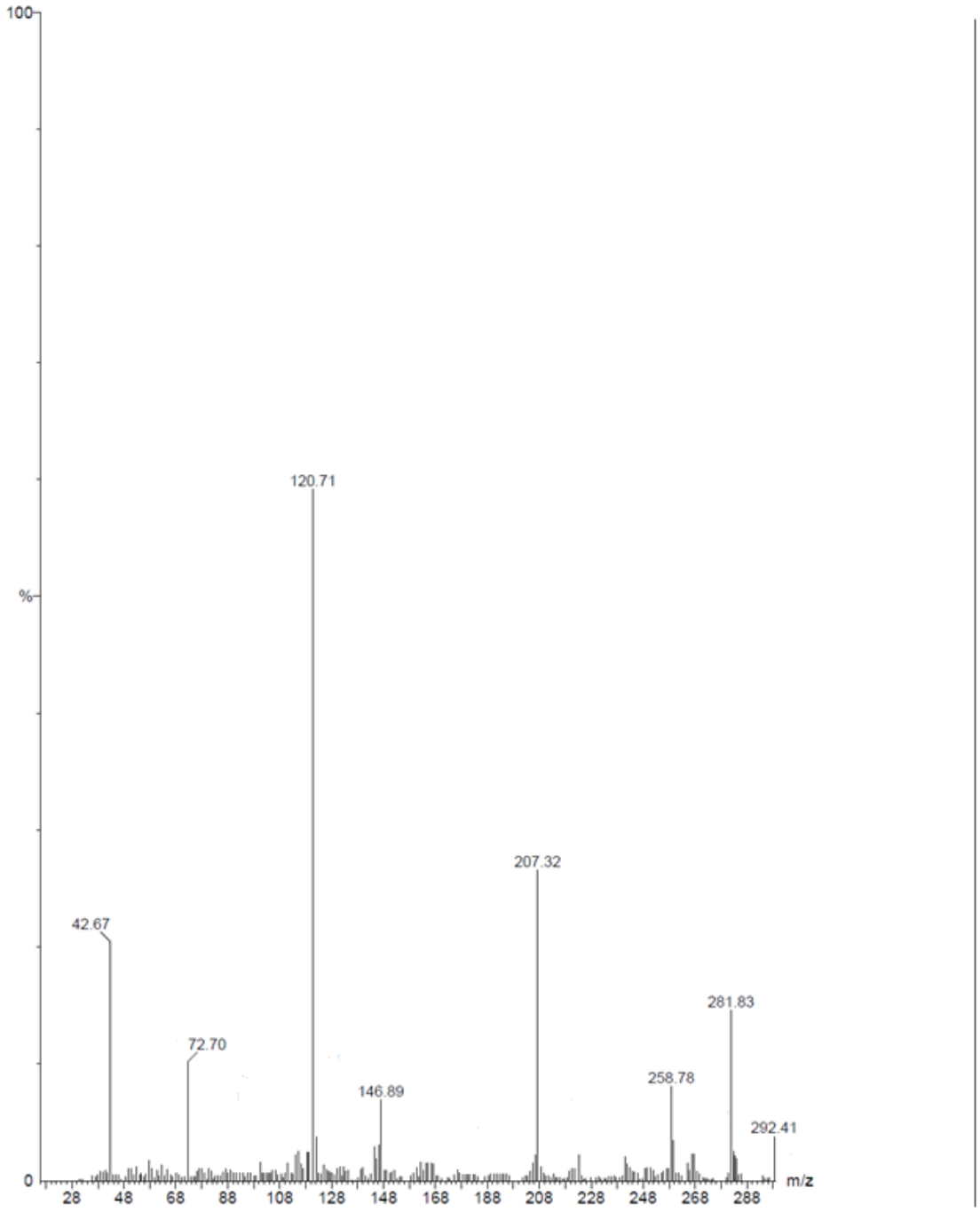
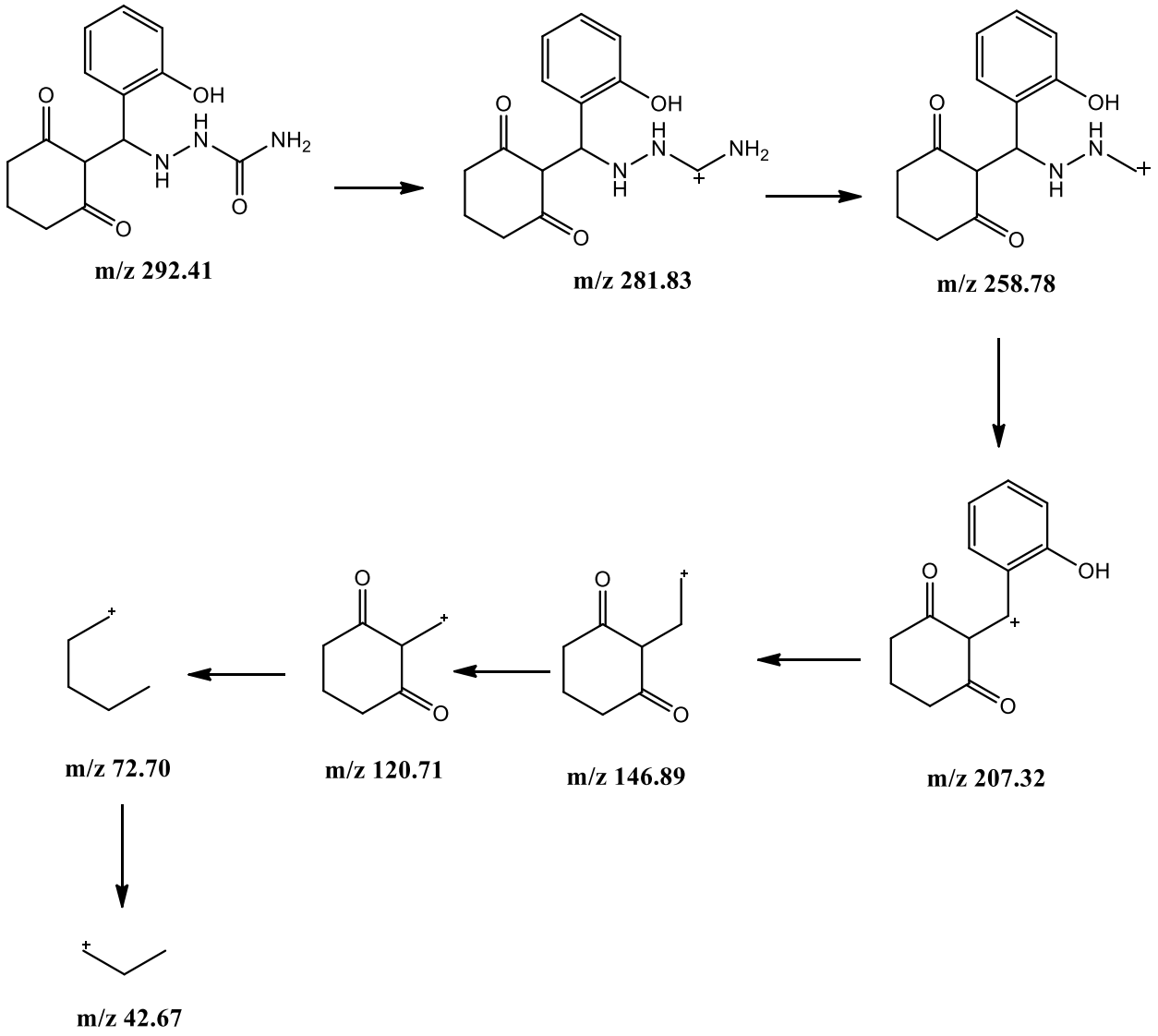


Fig. 22. Ligand (1)-Mass spectra



Mass spectral fragmentation pattern of Ligand 1.

5.1.6. IR Spectra

The existence of a strong band at 3435.94 and 1638.73cm^{-1}, which is attributed to vOH and the C=O carbonyl group, is a significant finding in the ligand spectrum (Fig. 23). The bands attributable to C=O and O-H moved towards lower

frequency in all of the complexes (Fig. 24-28), suggesting that carbonyl oxygen and hydroxyl oxygen were engaged in coordination through metal ions. In copper complex (**1a**), the M-O bond is represented by the new peak appeared at 757.42 cm^{-1}. The M-Cl bond is represented by the new peak at 526.68 cm^{-1}. The IR Spectral data of the complexes (**1a-1e**) and the ligand (**1**) were displayed in Table 4.

Table 4. IR Spectral data of the complexes (1a-1e) and the ligand (1)

Compound	IR stretching frequency (cm^{-1})			
	-OH	**-C=O**	**M-O**	**M-Cl**
Ligand (1)	3435.94	1638.73	-	-
Copper complex (1a)	3392.75	1633.69	757.42	526.68
Nickel complex (1b)	3465.32	1624.01	755.22	546.16
Iron complex (1c)	3416.11	1640.87	758.19	525.93
Chromium complex (1d)	3431.63	1633.14	757.24	525.14
Manganese complex (1e)	3437.60	1642.27	757.74	525.25

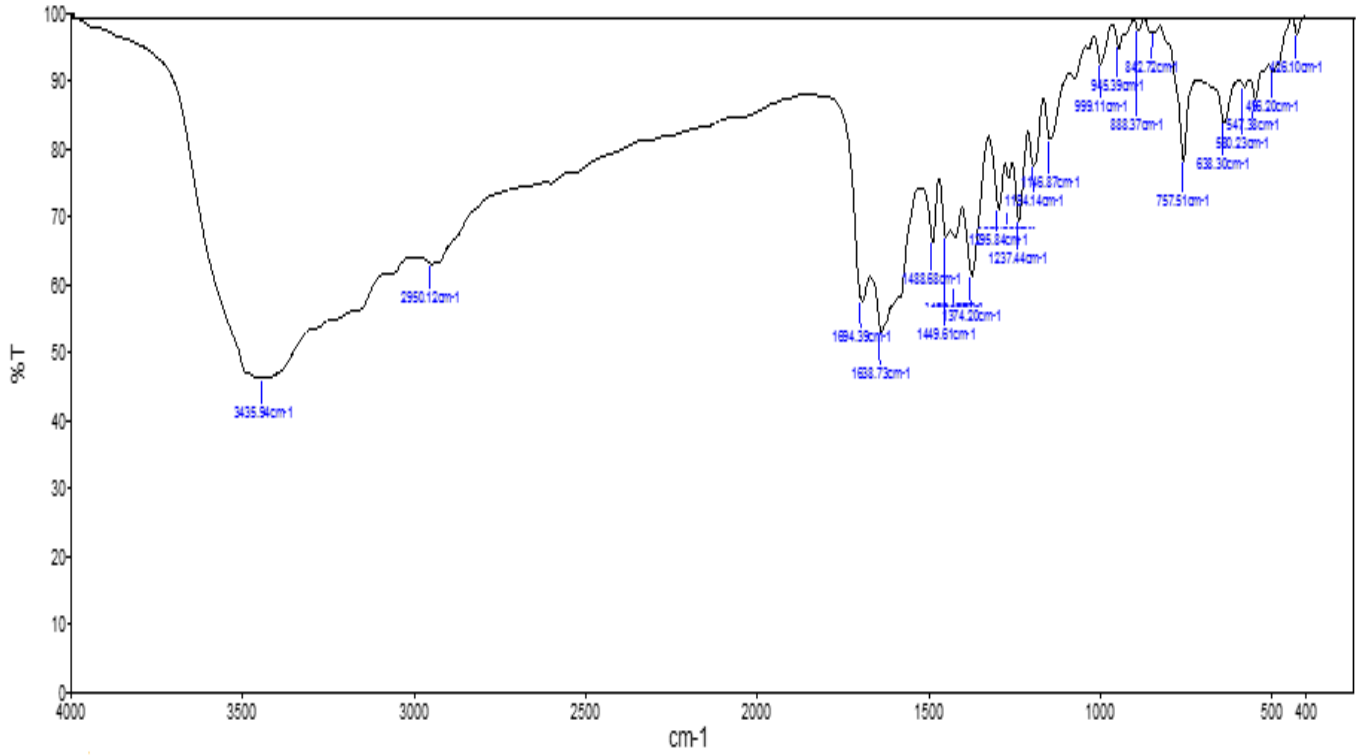


Fig. 23. Ligand (1) FT-IR spectra

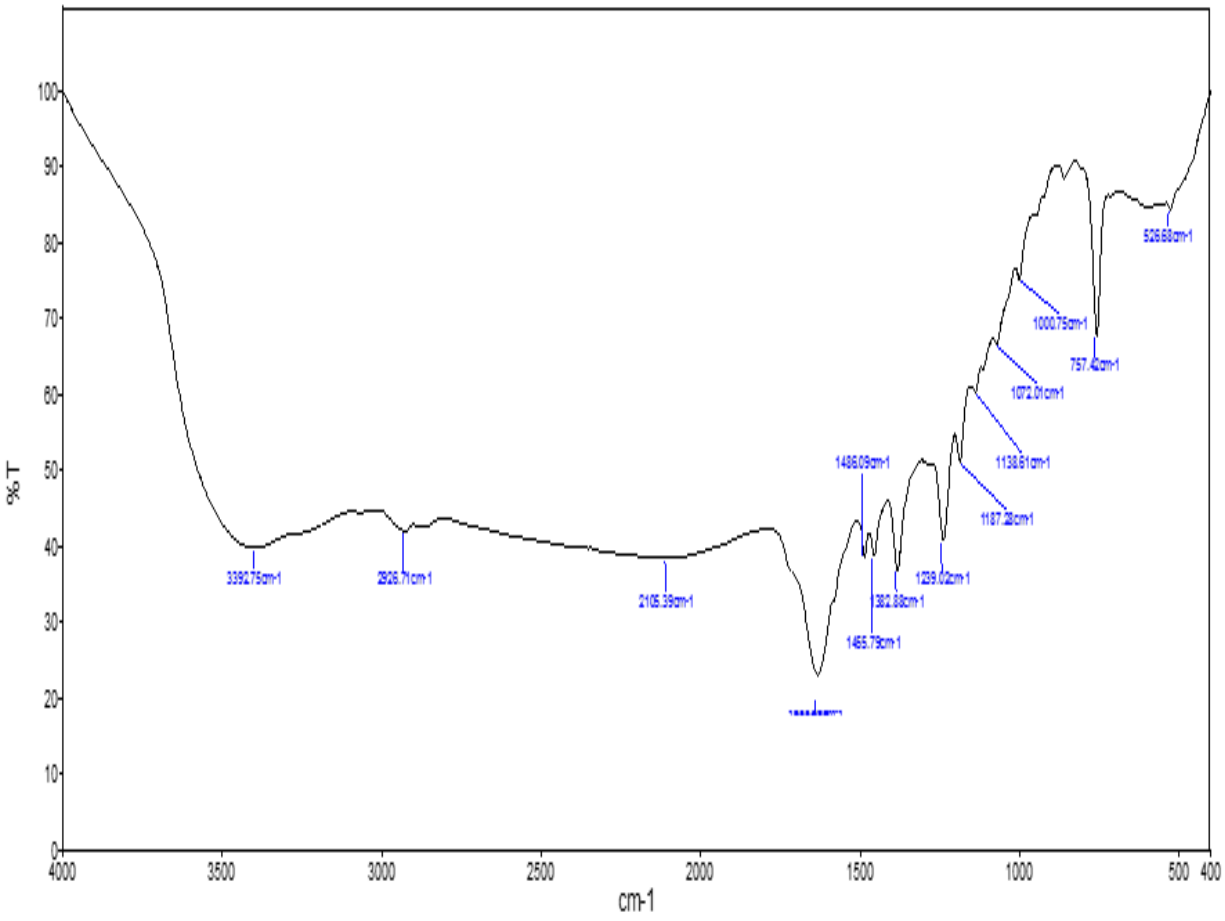


Fig. 24. Copper complex (1a) FT-IR spectra

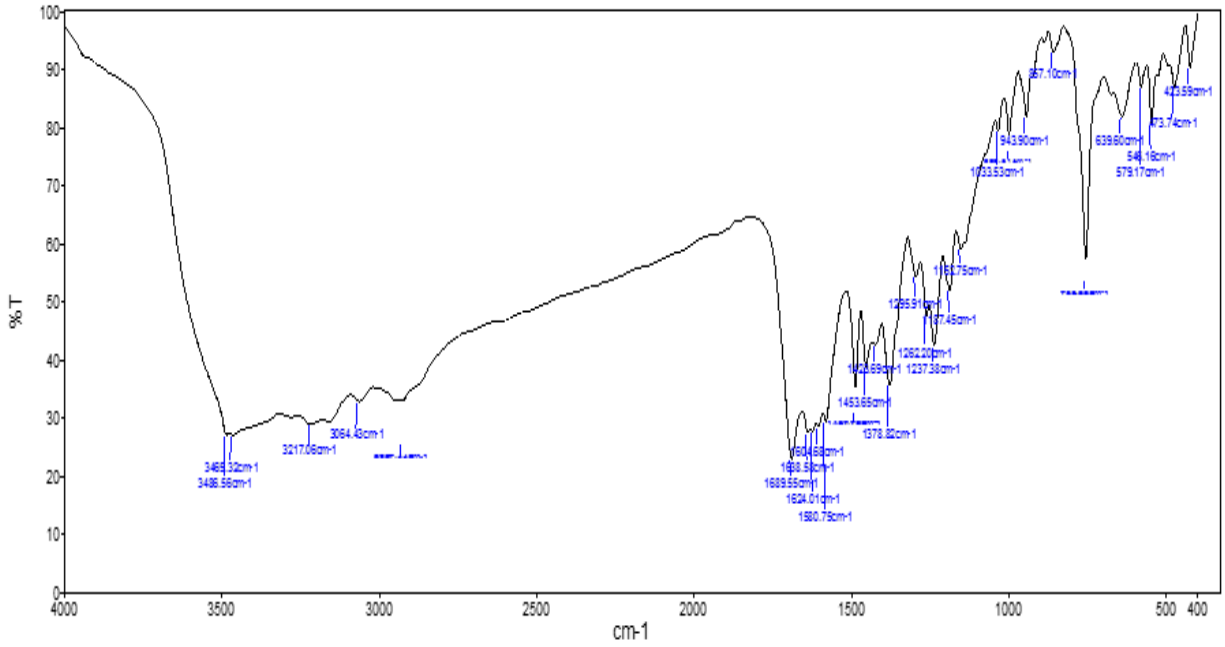


Fig. 25. Nickel complex (1b) FT-IR spectra

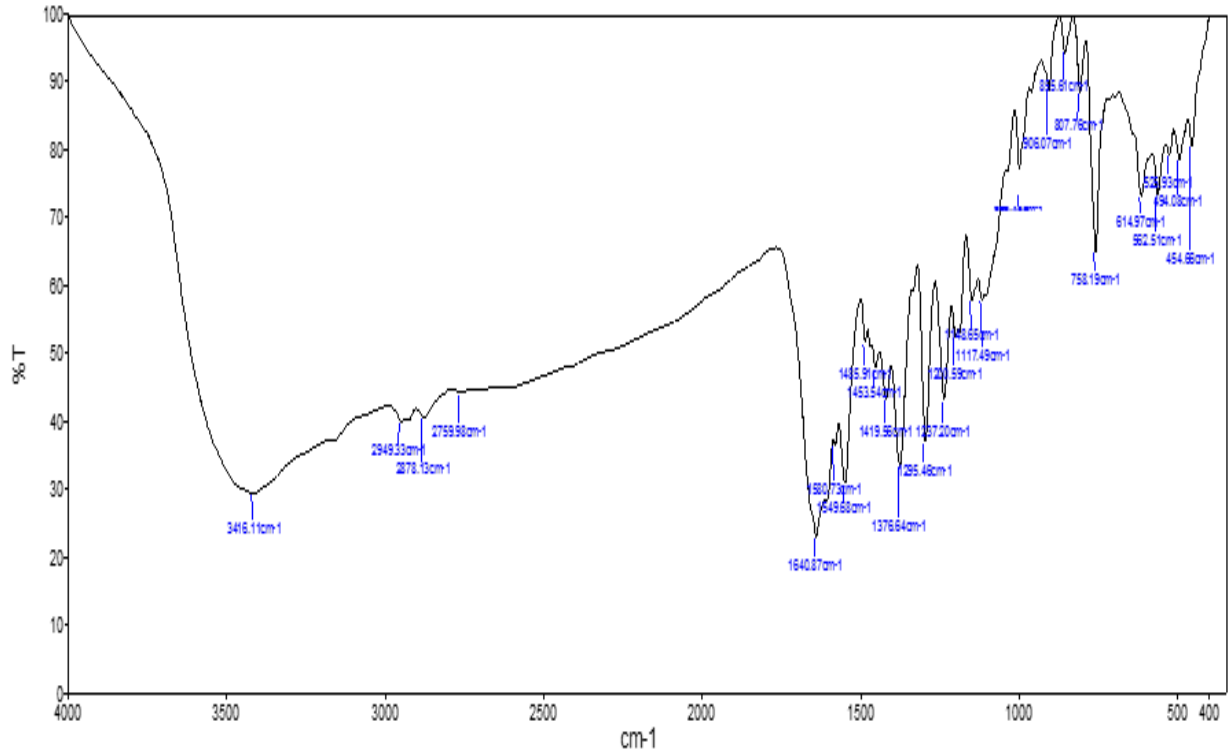


Fig. 26. Iron complex (1c) FT-IR spectra

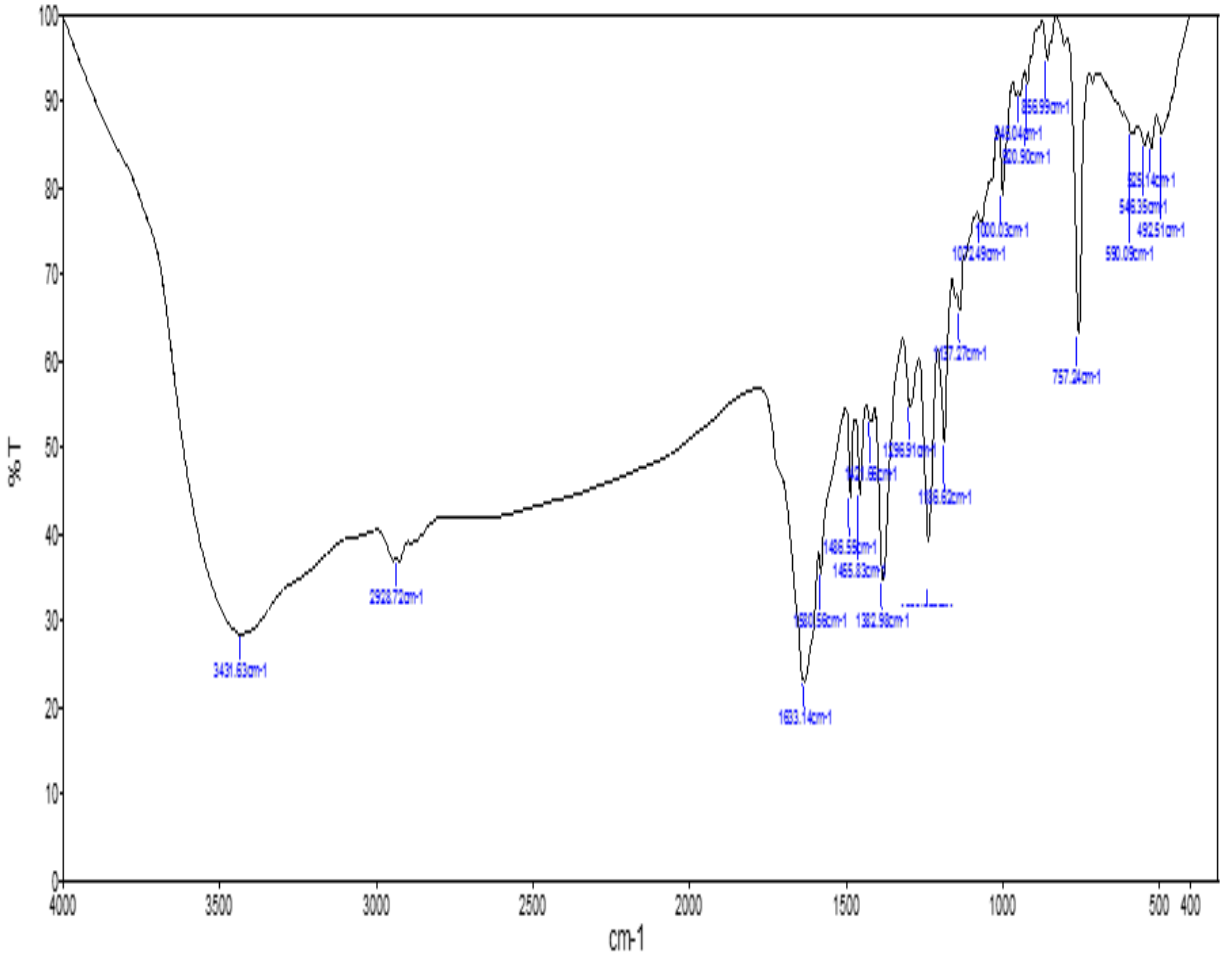


Fig. 27. Chromium complex (1d) FT-IR spectra

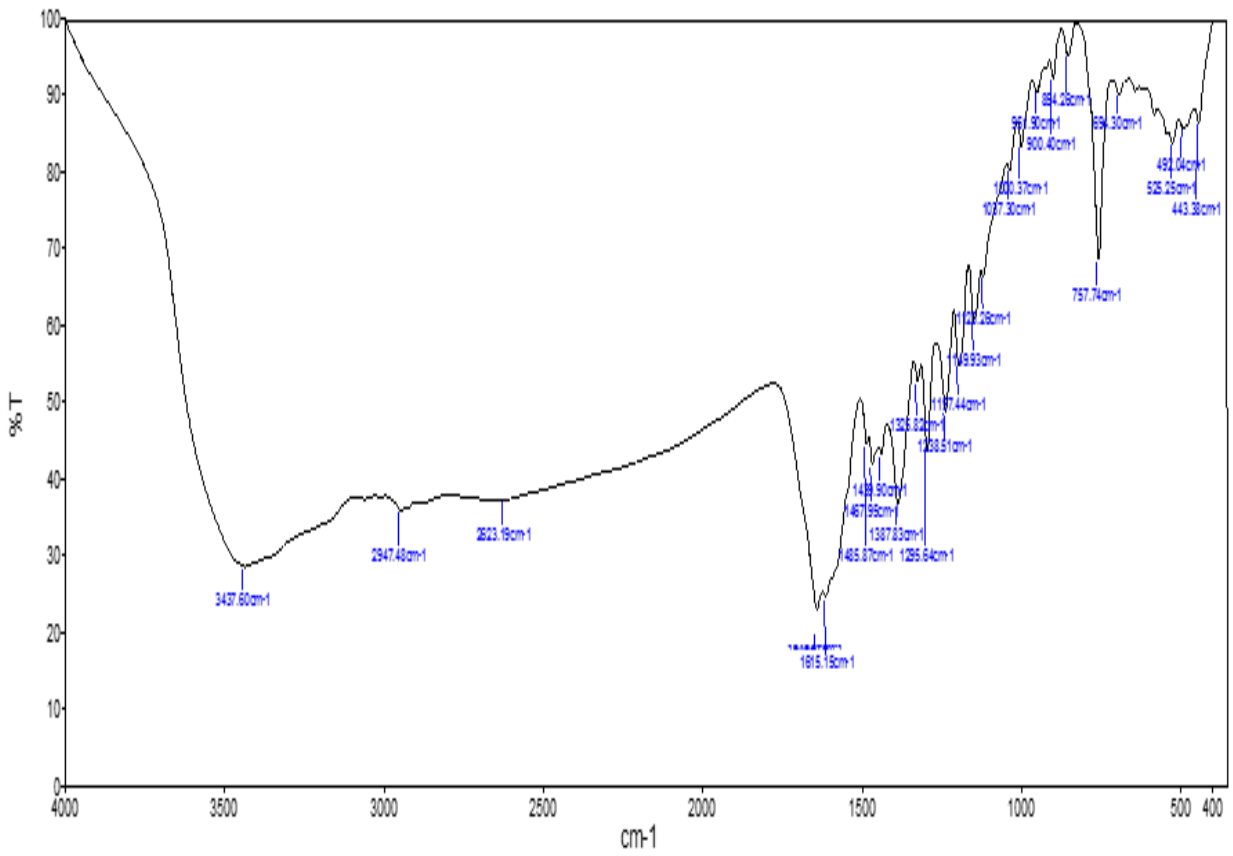


Fig. 28. Manganese complex (1e) FT-IR spectra

5.1.7. UV-Visible Spectra

The ligand and complex UV-visible spectra were obtained in the region of 100-1100 nm. The UV spectra of ligand (1) primarily revealed two strong maximum bands at 380nm and 525nm, which correspond to the π →π* and n →π* transitions, respectfully (Fig. 29). The octahedral geometry of the Cu (II) complex being investigation is suggested by a wide band in the 300nm range. The octahedral structure of the Ni (II) complex was confirmed by wide peaks at 263nm and 311nm. The octahedral structure of the bands found for Cr (II) complex also displays wide

peaks at 263nm and 301nm. Broad signals were seen at 263nm and 321nm for the Fe (II) complex, confirming its octahedral shape. The Mn (II) complex emitted wide signals at 262 nm, indicating that it is octahedral. Fig. 30-34 shows the UV spectrums of metal complexes (**1a-1e**).

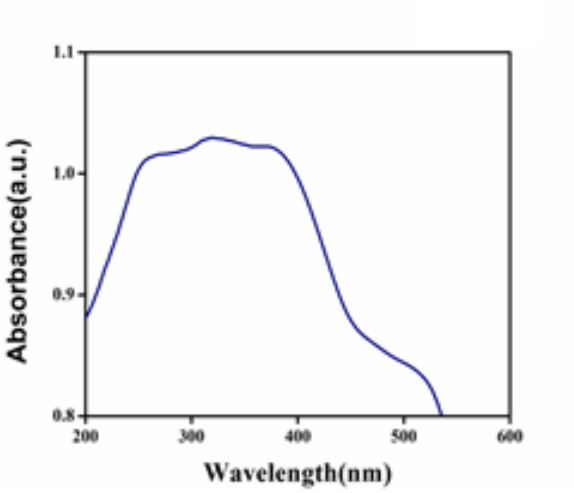


Fig. 29. Ligand 1 UV-spectra

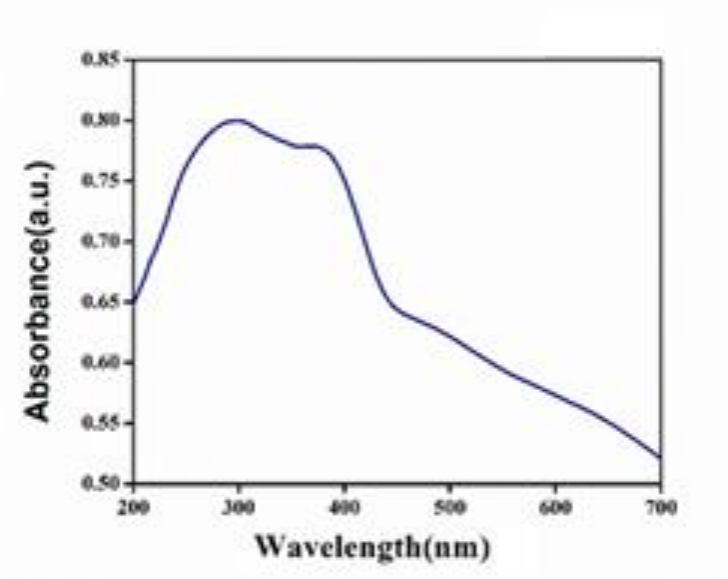


Fig. 30. Copper complex (1a) UV-Spectra

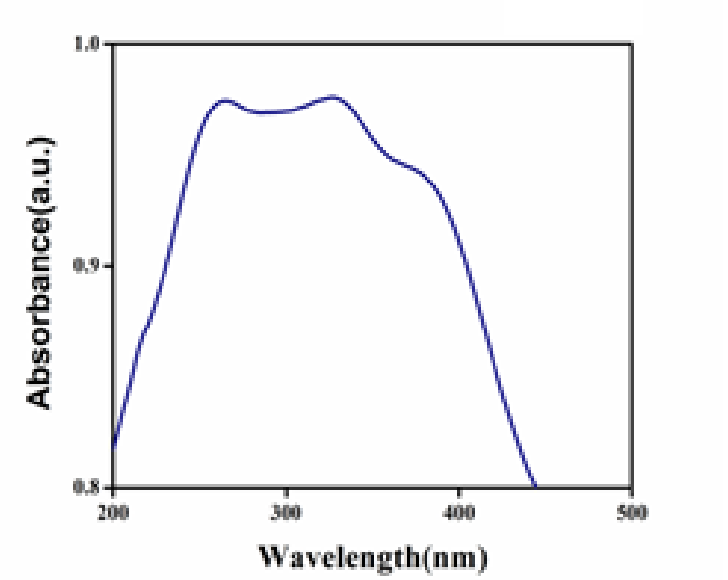


Fig. 31. Nickel complex (1b) UV-Spectra

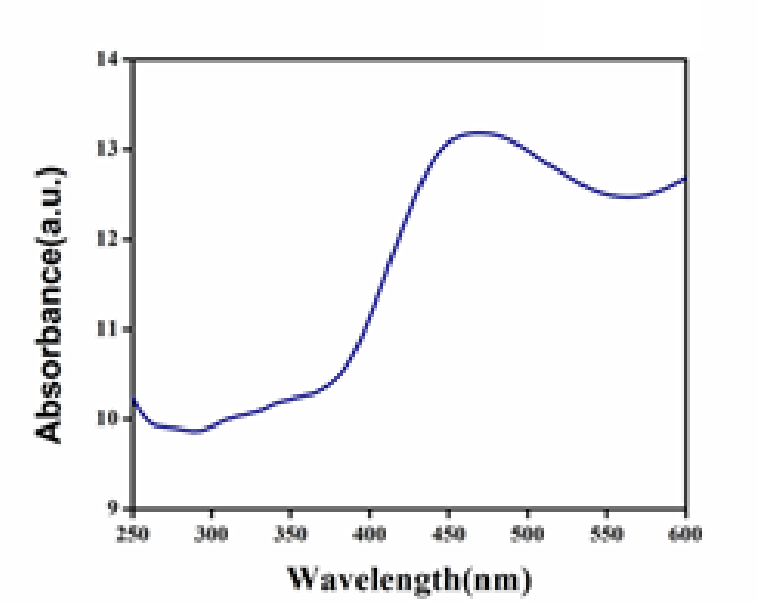


Fig. 32. Iron complex (1c) UV-Spectra

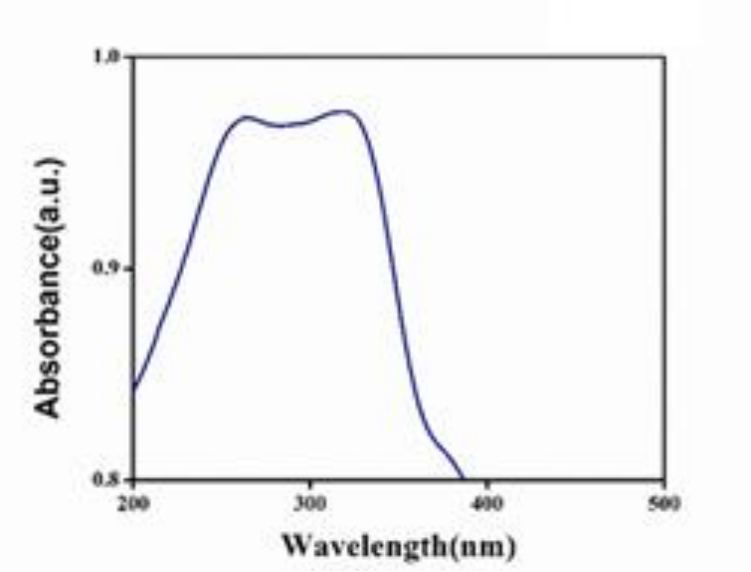


Fig. 33. Chromium complex (1d) UV-Spectra

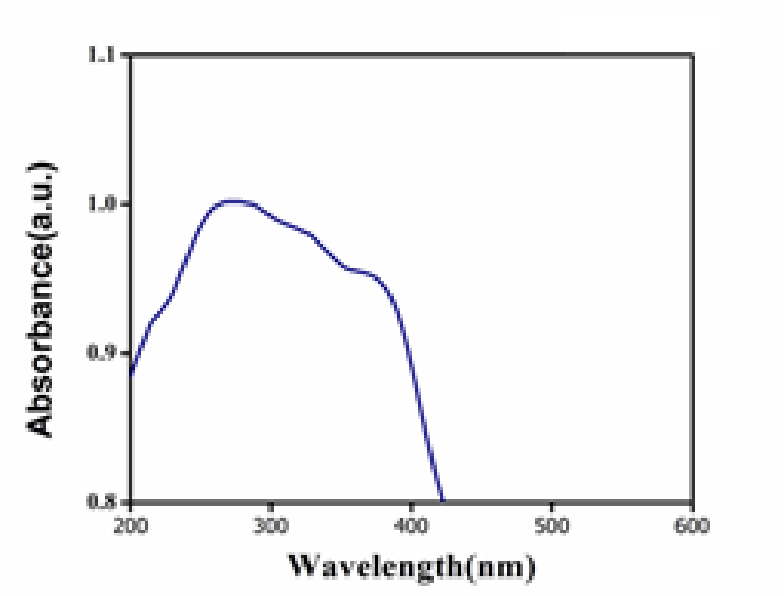


Fig. 34. Manganese complex (1e) UV-Spectra

5.1.8. EPR spectra

The type of metal ligand bond formation along with the dispersion of paired and unpaired electrons may be learned through EPR spectrum analysis. Cu (II) complexes have a unique character in coordination chemistry, with geometries such as tetrahedral, square planar, octahedral, and square pyramidal that may be distinguished by EPR spectrometry. $g_{\parallel}$, $g_{\perp}$, gavg and G are EPR parameters that indicate if the compound is octahedral or tetrahedral. The following criterion confirms the existence of an unpaired electron in the dx^2-y^2 orbital: $g_{\parallel} > g_{\perp} > 2.0023$. For the copper complex, the measured $g_{\parallel}$ and $g_{\perp}$ values are 2.1581 and 2.0138, correspondingly. The ionic nature is shown by a $g_{\parallel}$ value more than 2.3, while the covalent nature is indicated by a $g_{\parallel}$ value less than 2.3. We can see that

the g‖ value (2.1581) is smaller than 2.3, indicating that the compound is covalent. According to Hathaway, G values less than four indicate a significant exchange contact between metal centers, whereas G values higher than four indicate a minimal charge transfer. The G value is 4.76 in this case, thus the exchange interaction is insignificant. The Cu (II) complex exhibits deformed octahedral geometry, according to the EPR characteristics. The EPR spectra of copper complex (**1a**) was shown in Fig. 35.

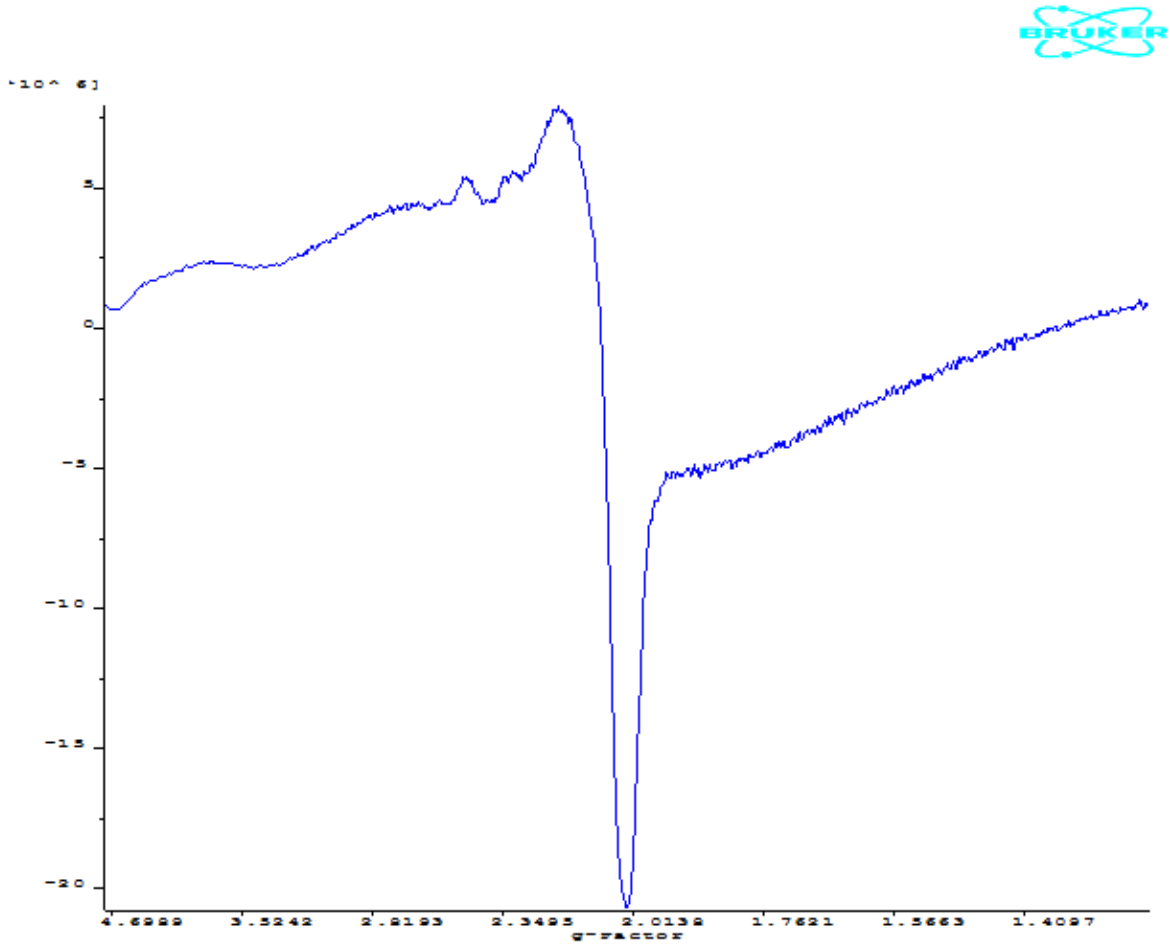
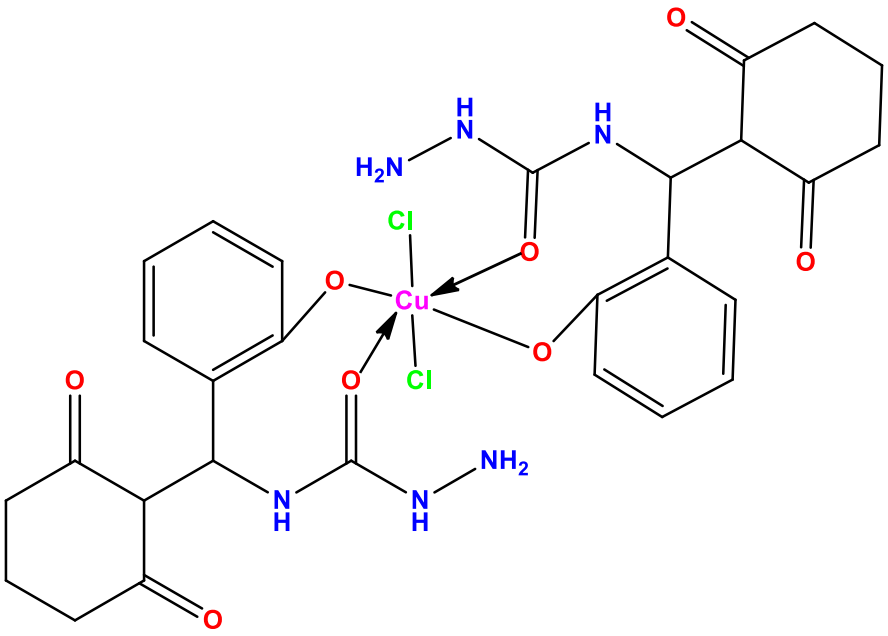


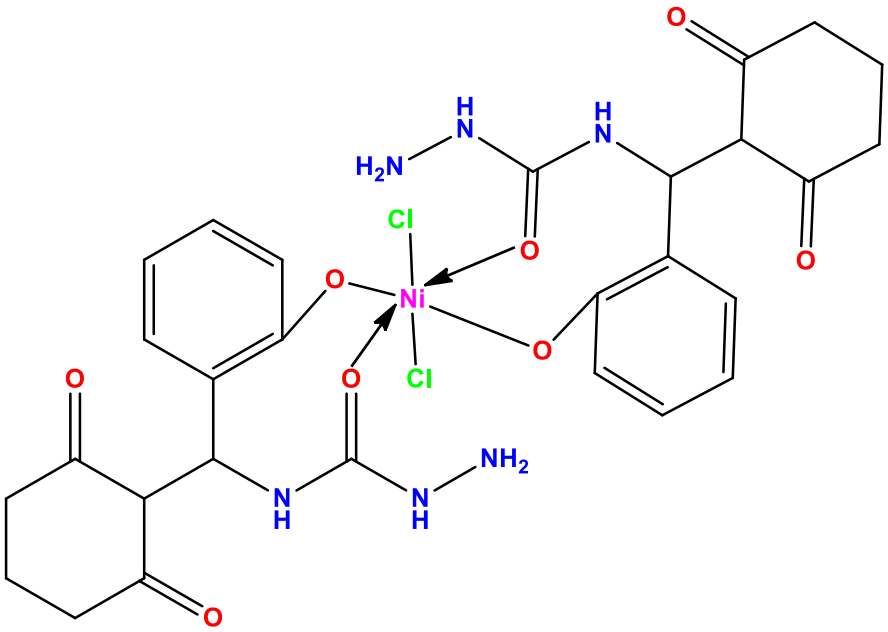
Fig. 35. Copper complex (1a) EPR spectra

5.1.9. Suggested Structure of the Complexes

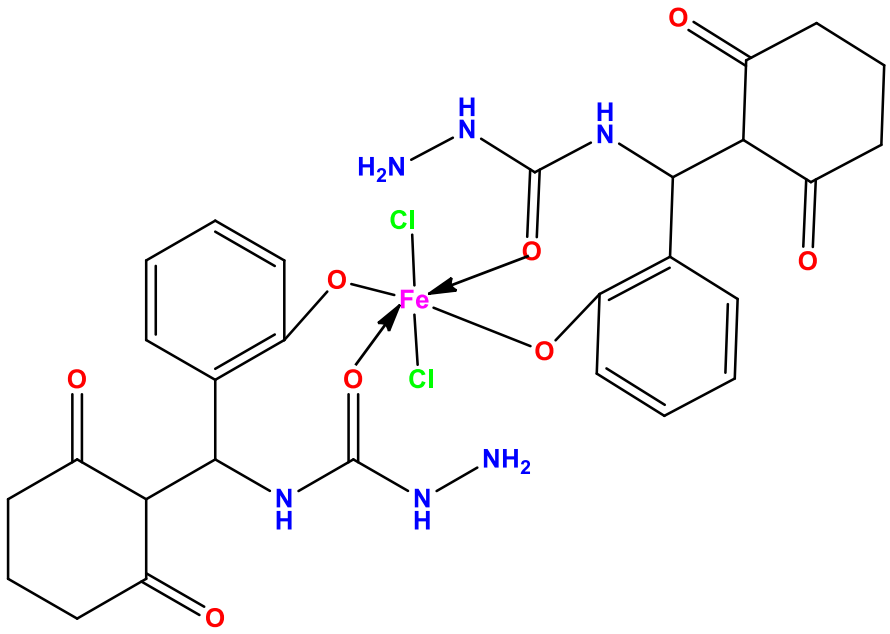
We propose the following structure of complexes produced with the Mannich base ligand based on the preceding findings.



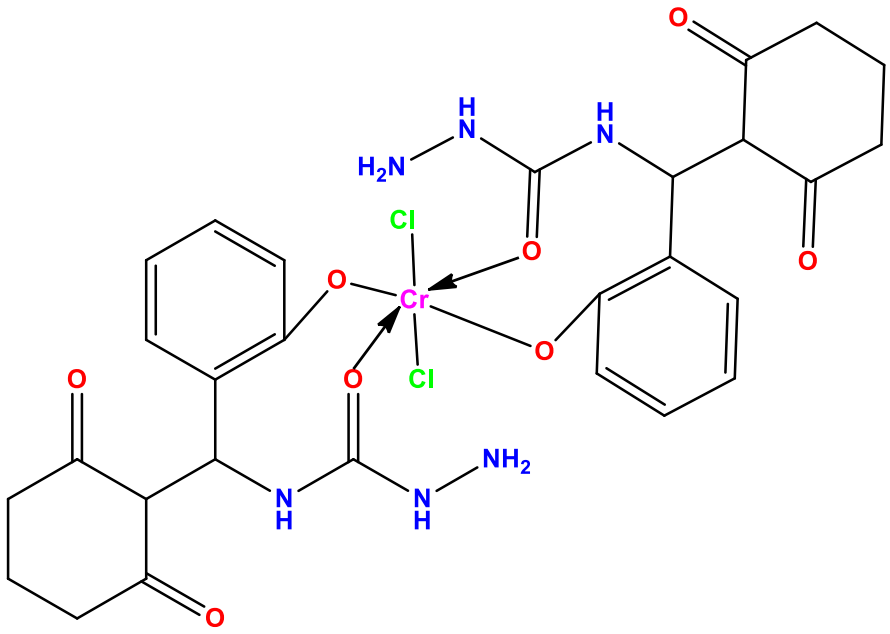
Structure of the Copper complex (1a) with ligand 1



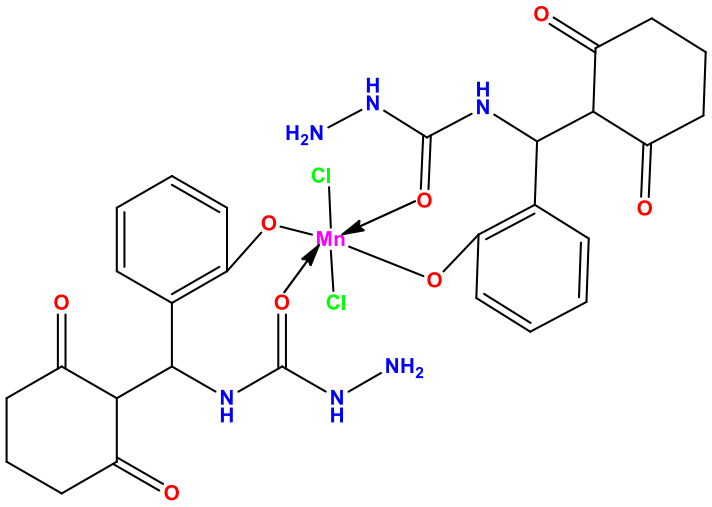
Structure of the Nickel complex (1b) with ligand 1



Structure of the Iron complex (1c) with ligand 1



Structure of the Chromium complex (1d) with ligand 1



Structure of the Manganese complex (1e) with ligand 1

5.2. Metal complexes (2a-2e) with ligand (2)

5.2.1. Physical properties

Table 5 shows the physical properties of the ligand (**2**) as well as the complexes (**2a-2e**) generated from it.

Table 5. Physical possessions of complexes (2a-2e) and its ligand (2)

Compound	Color	Melting point (ºC)
Ligand (2)	Dust white	146
Copper complex (2a)	Blue	162
Nickel complex (2b)	Pale green	142
Iron complex (2c)	Brown	154
Chromium complex (2d)	Green	160
Manganese complex (2e)	White	172

5.2.2. Solubility

The solubility of the ligand (**2**) and the complexes (**2a-2e**) in various solvents was investigated, and the findings are shown in Table 6. The metal complexes (**2a-2e**) derived from ligand (**2**) dissolve more readily in aprotic solvents than in protic solvents, according to solubility experiments (Table 6).

Table 6. Solubility test results of complexes (2a-2e) and its ligand (2)

Compound	Water	Ethanol	Chloroform	DMSO
Ligand (2)	Insoluble	Insoluble	Sparingly soluble	Soluble
Copper complex (2a)	Insoluble	Insoluble	Insoluble	Soluble
Nickel complex (2b)	Insoluble	Insoluble	Insoluble	Soluble
Iron complex (2c)	Insoluble	Insoluble	Insoluble	Soluble
Chromium complex (2d)	Insoluble	Insoluble	Insoluble	Soluble
Manganese complex (2e)	Insoluble	Insoluble	Insoluble	Soluble

5.2.3. Conductivity and magnetic susceptibility measurements

Various solvents, including water, ethanol, chloroform, and DMSO, were used to test the solubility of the newly synthesized metal complexes. The Equiptronics digital conductivity meter (Model EQ-660) was used to determine molar conductance in DMSO, with the cell constant calibrated using 0.1M KCl solution. The electrical conductivity of a 10^{-3} M solutions of respective complexes (2a-2e) in DMSO was determined, revealing the complexes' neutral (non-electrolytic) character. The molar conductance of the mixed ligand complexes of ligand (2) ranges from 17 to 26 $\Omega^{-1}mol^{-1}cm^{2}$. The chloride ions were shown to be coupled to metal ions via conductivity tests, suggesting that they function as ligands rather than ions. Combinations for the produced complexes were allocated based on the metal – ligand ratio (1:2) and the characteristics of the electrolytes as determined by conductance measurements, which aids in describing the structure of the complex. The Conductance and magnetic properties of metal complexes (**2a-2e**) with ligand (**2**) were shown in Table 7.

Table 7. Conductance and magnetic properties of metal complexes (2a-2e) with ligand (2)

S. No	Compounds	Conductance ($\Omega^{-1}mol^{-1}cm^{2}$)	Magnetic Susceptibility (μ_{eff}. B.M)
1.	Copper complex (2a)	17	2.25
2.	Nickel complex (2b)	26	3.70
3.	Iron complex (2c)	23	5.64
4.	Chromium complex (2d)	20	4.82
5.	Manganese complex (2e)	21	5.34

5.2.4. NMR Spectra of ligand (2)

The hydrogens of the aromatic rings show a multiplet at 7.12-6.90 ppm in the ^{1}H NMR spectrum of the Mannich base ligand (**2**) during investigation (Fig. 36). The methylene hydrogens linked to the salicylaldehyde and amine hydrogens of the urea show as a peak at 4.22 ppm, whereas the aromatic –OH occurs at 5.30 ppm. The ligand's creation is also determined by the change in a signal equivalent to the secondary amine $–NH_2$ proton of because it was removed in the Mannich process. The carbons of the aromatic rings had peaks at 130.19-115.75 ppm in the ^{13}C NMR spectra of the Mannich base ligand (**2**) in investigation (Fig. 37). The presence of a peak at 56.01 ppm shows that the methylene carbon is linked to the salicylaldehyde and urea's amine hydrogens. Furthermore, the carbonyl carbons of the 1,3-

cyclohexanedione and urea constituent are represented by the peaks at 208.83 and 162.72 ppm, respectively.

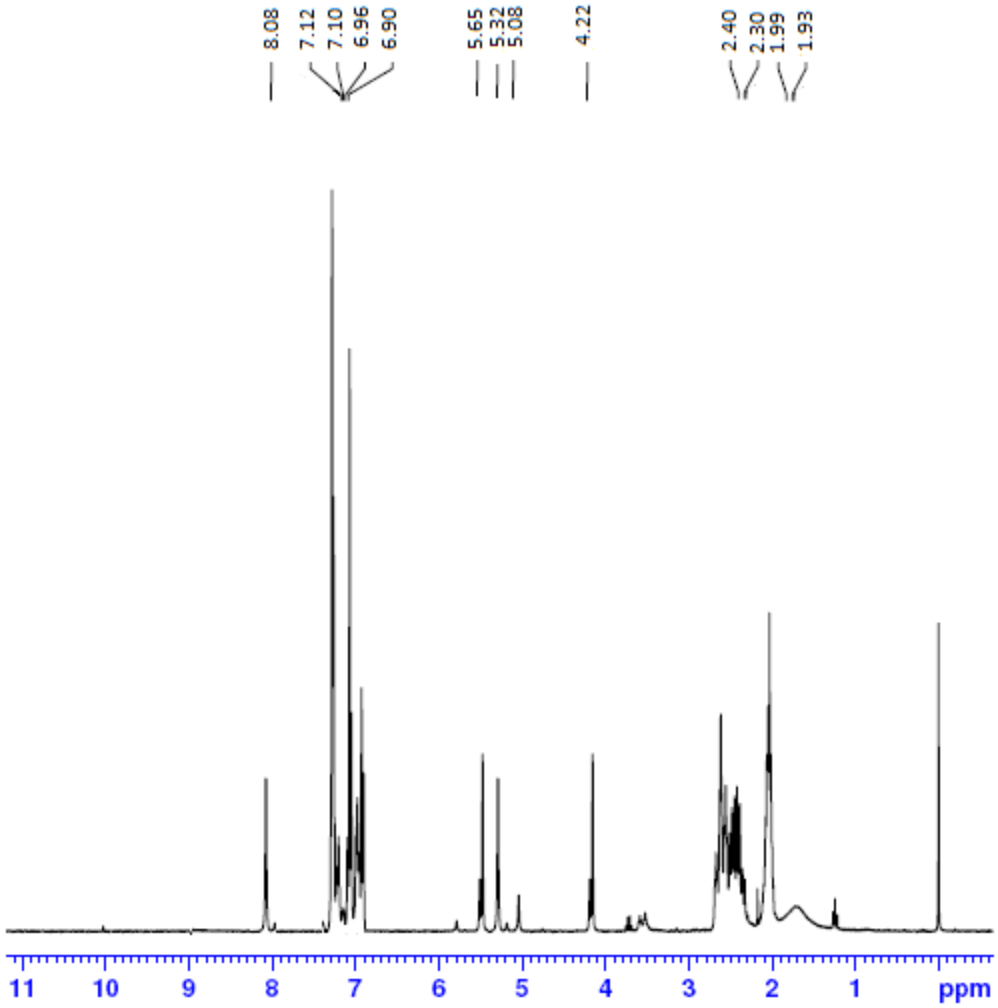


Fig. 36. Ligand (2)-^{1}H-NMR spectrum

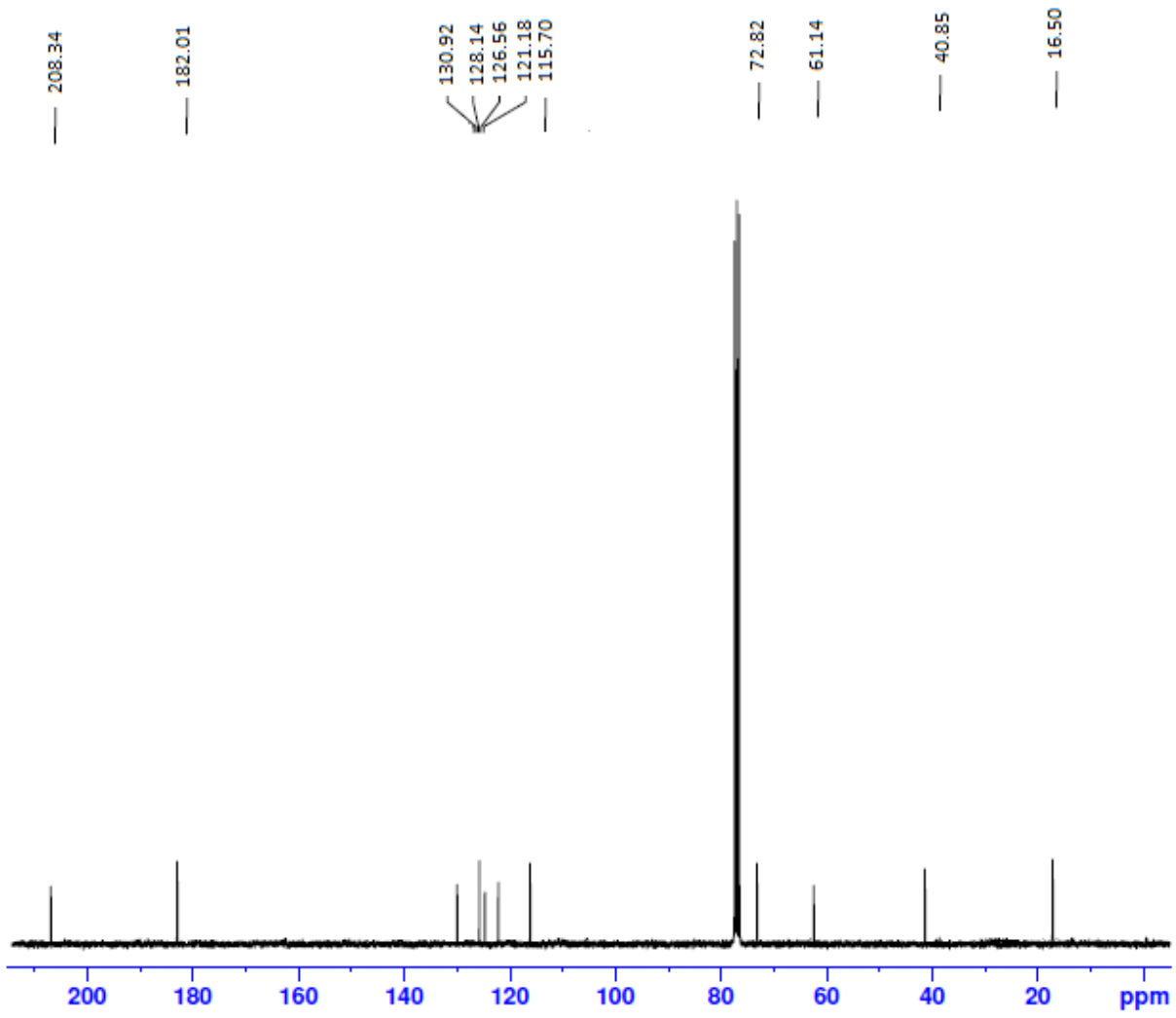


Fig. 37. Ligand (2)-^{13}C-NMR spectrum

5.2.5. Mass Spectral studies of ligand (2)

The mass spectrum of the Mannich base ligand (**2**) below investigation (Fig. 38). The observed molecular weight of ligand (**2**) is 276.29 and that was confirmed by mass spectral studies at m/z 277.38. The molecular ion peak appeared at m/z

43.70. The other fragmentation peasks were m/z 206.93, 152.14 and 122.63 respectively.

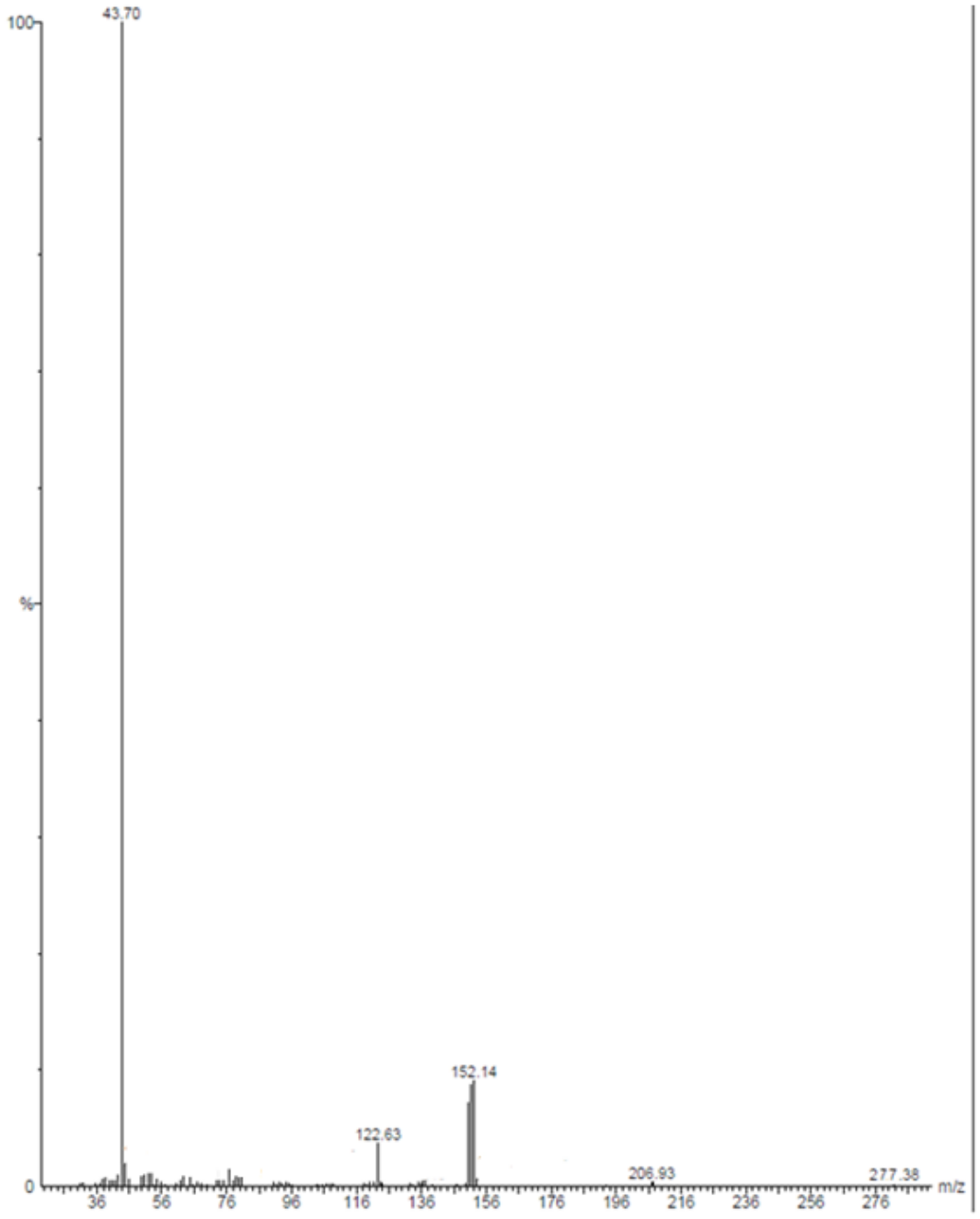
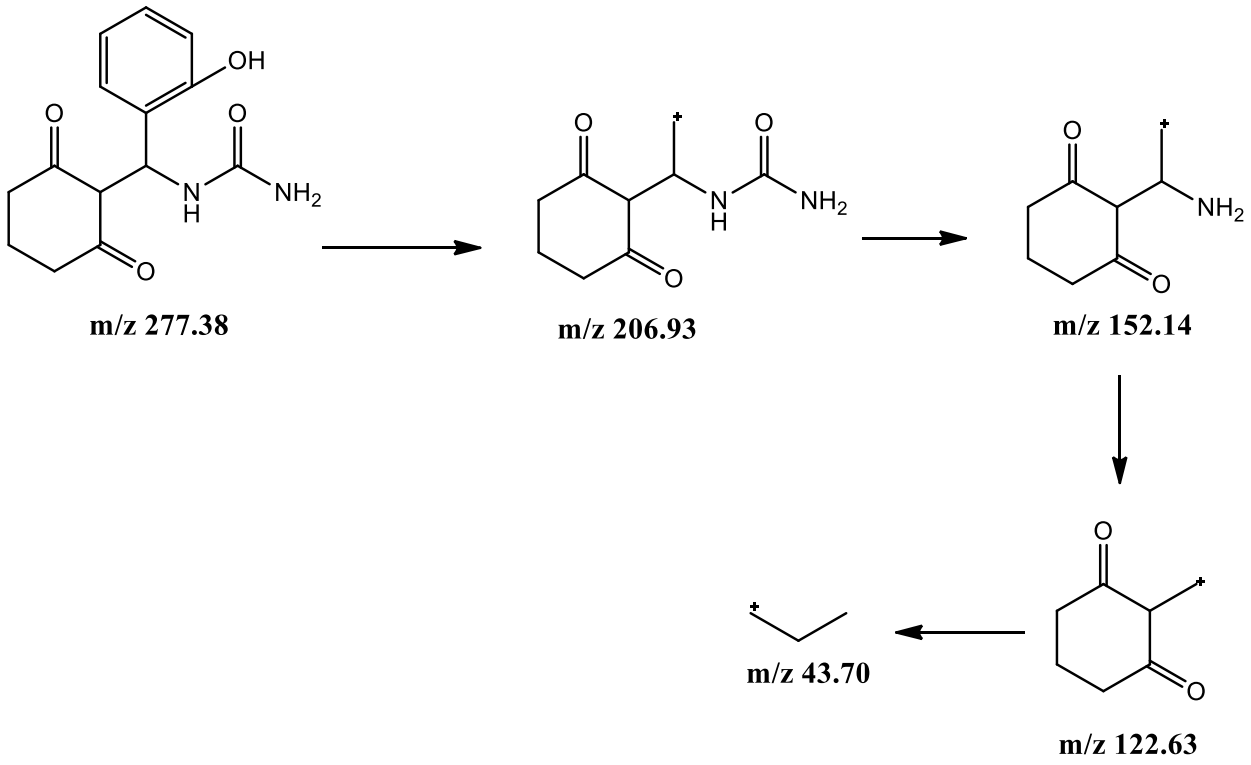


Fig. 38. Ligand (2)-Mass spectra



Mass spectral fragmentation pattern of Ligand 2.

5.2.6. IR Spectra

The existence of a strong band at 3436.28 and 3076.43 cm^{-1}, which would be attributable to the vO-H and N-H groups, is a significant finding in the ligand spectrum (Fig. 39). The bands attributable to O-H and N-H moved towards lower frequency in all the complexes (Fig 40-44), suggesting that oxygen and nitrogen were engaged in coordination between metal ions. In copper complex (**2a**), the M-N bond is represented by the new peak appeared at 855.81 cm^{-1}. The M-O bond is

represented by the new peak at 758.11 cm^{-1}. At 493.66 cm^{-1}, there are new bands, which corresponds to the M-Cl bond. The IR Spectral data of complexes (2a-2e) and the ligand (2) were displayed in Table 8.

Table 8. IR Spectral data of complexes (2a-2e) and the ligand (2)

Compound	IR stretching frequency (cm^{-1})				
	-OH	**-N-H**	**M-N**	**M-O**	**M-Cl**
Ligand (2)	3436.28	3076.46	-	-	-
Copper complex (2a)	3450.43	2950.60	855.81	758.11	493.66
Nickel complex (2b)	3449.65	2950.60	851.78	771.18	493.95
Iron complex (2c)	3440.23	3077.30	854.63	774.91	494.62
Chromium complex (2d)	3450.41	2950.95	854.18	774.95	494.63
Manganese complex (2e)	3429.49	3077.24	853.62	759.76	493.88

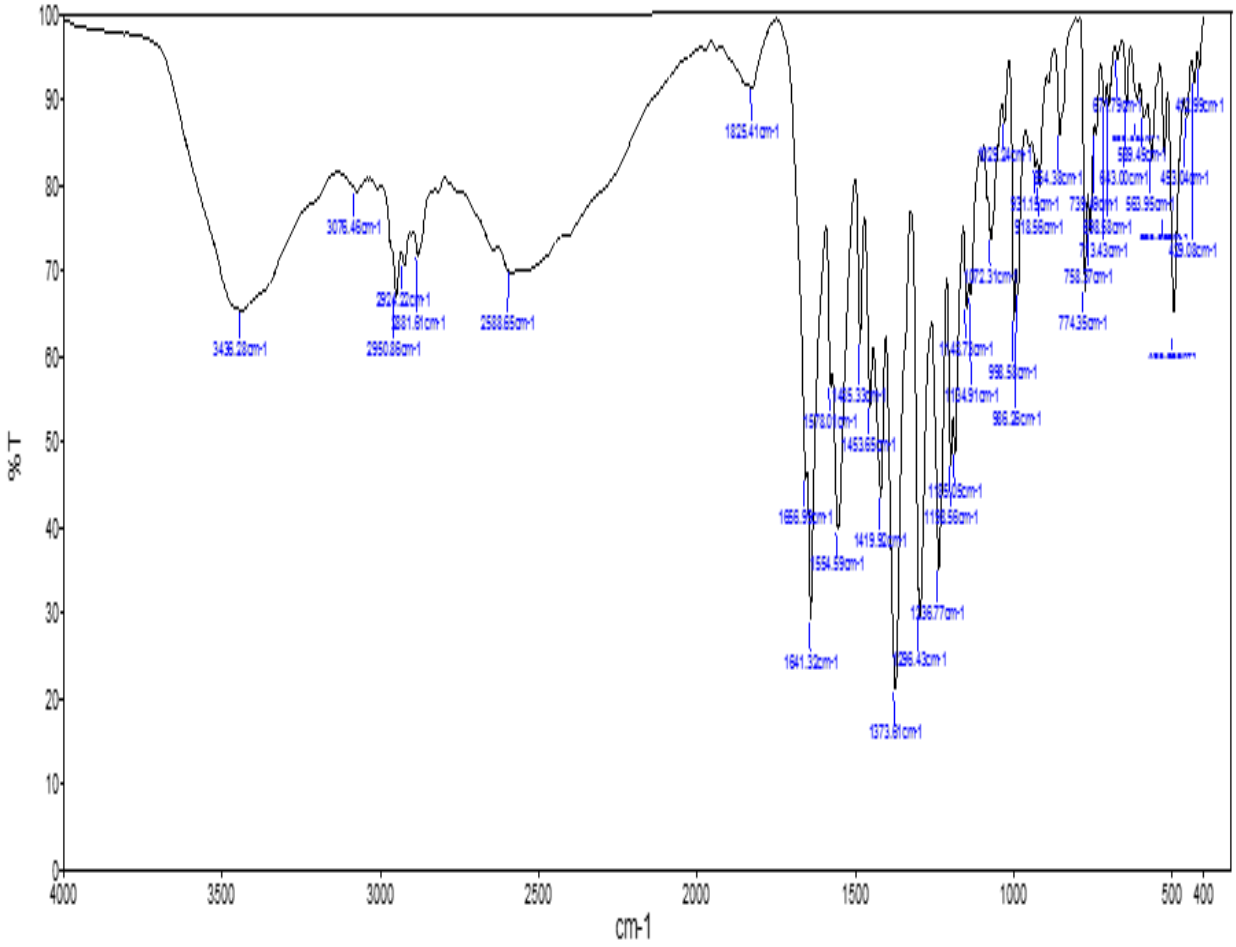


Fig. 39. Ligand (2)-FT-IR spectra

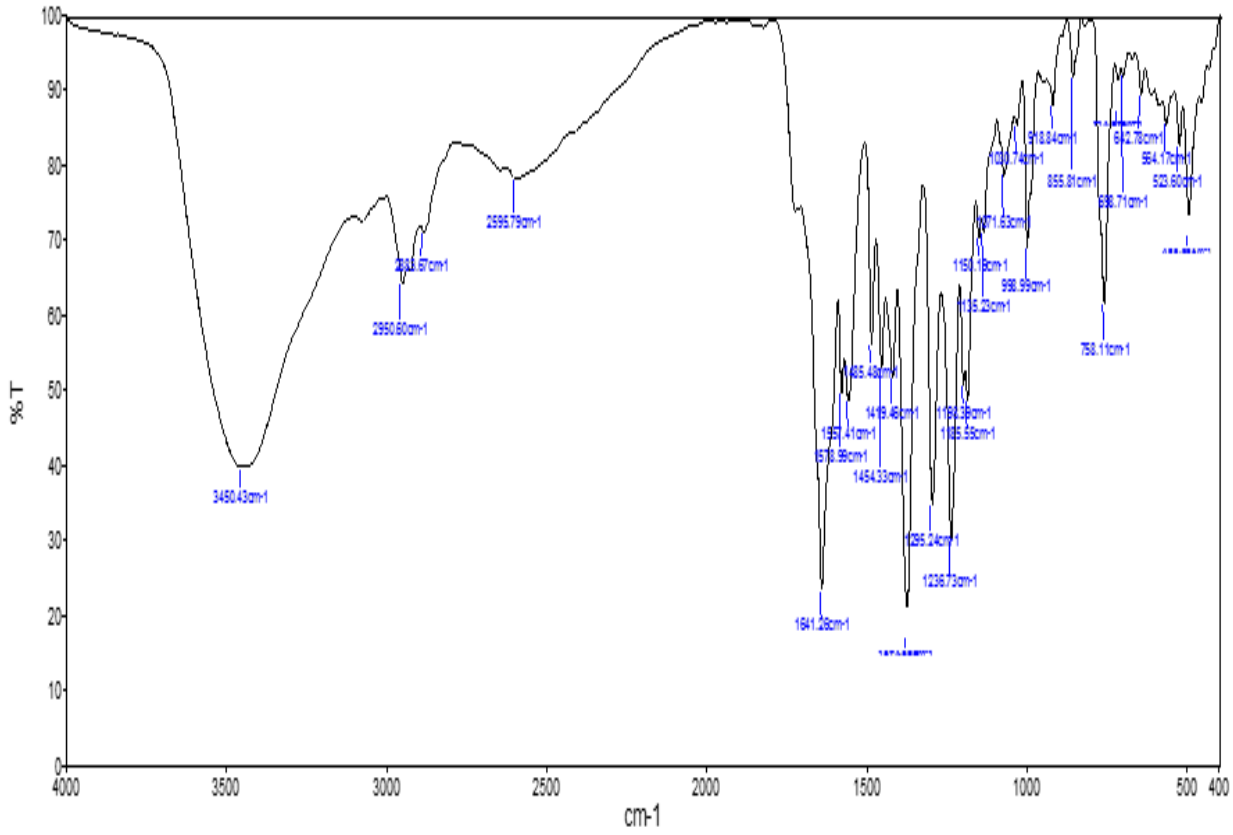


Fig. 40. Copper complex (2a)-FT-IR spectra

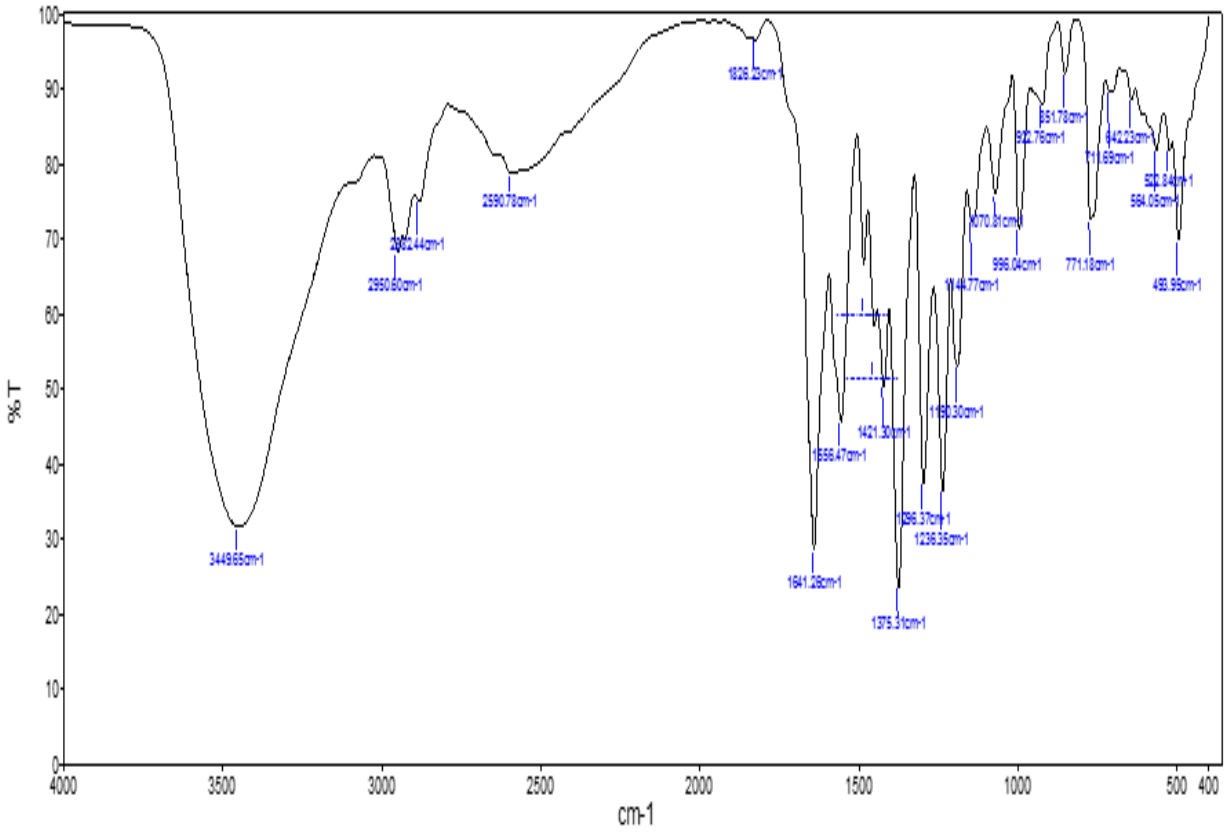


Fig. 41. Nickel complex (2b)-FT-IR spectra

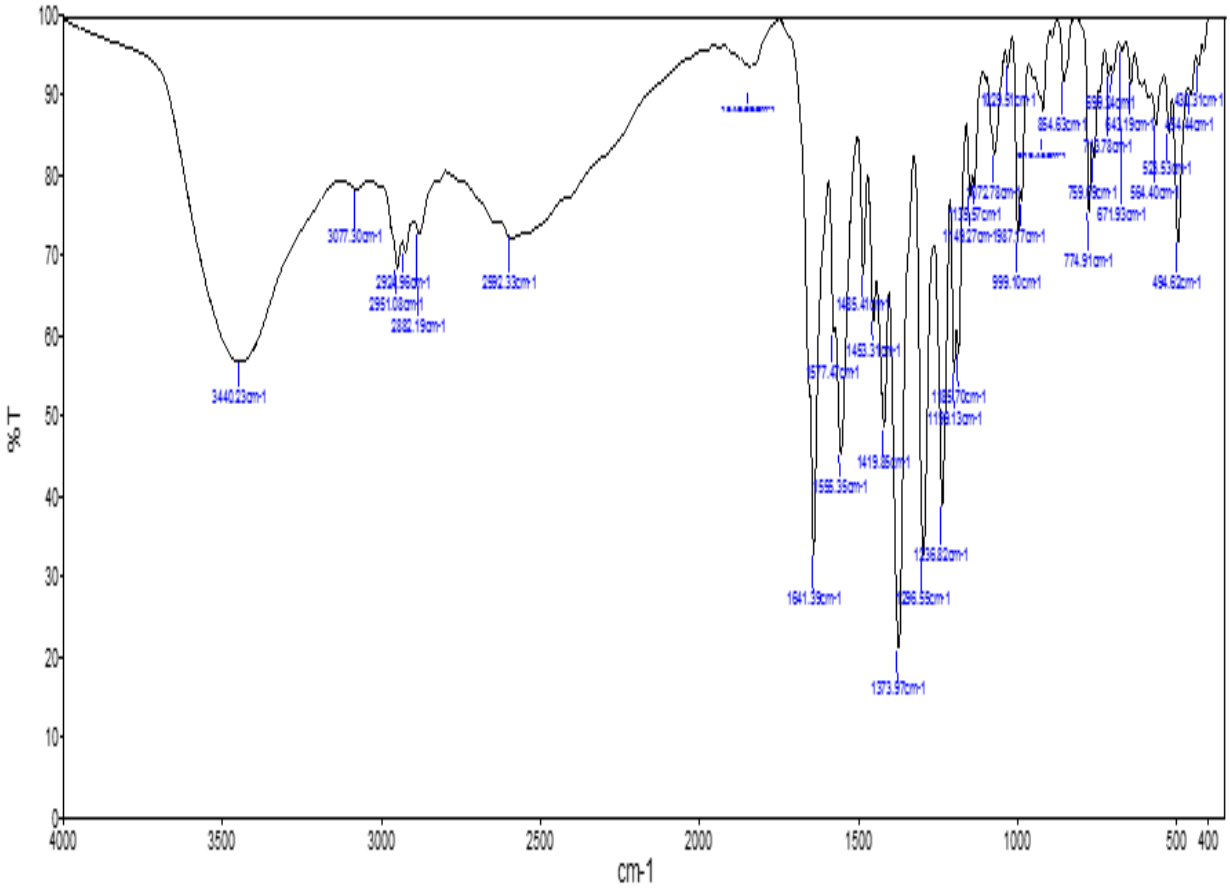


Fig. 42. Iron complex (2c)-FT-IR spectra

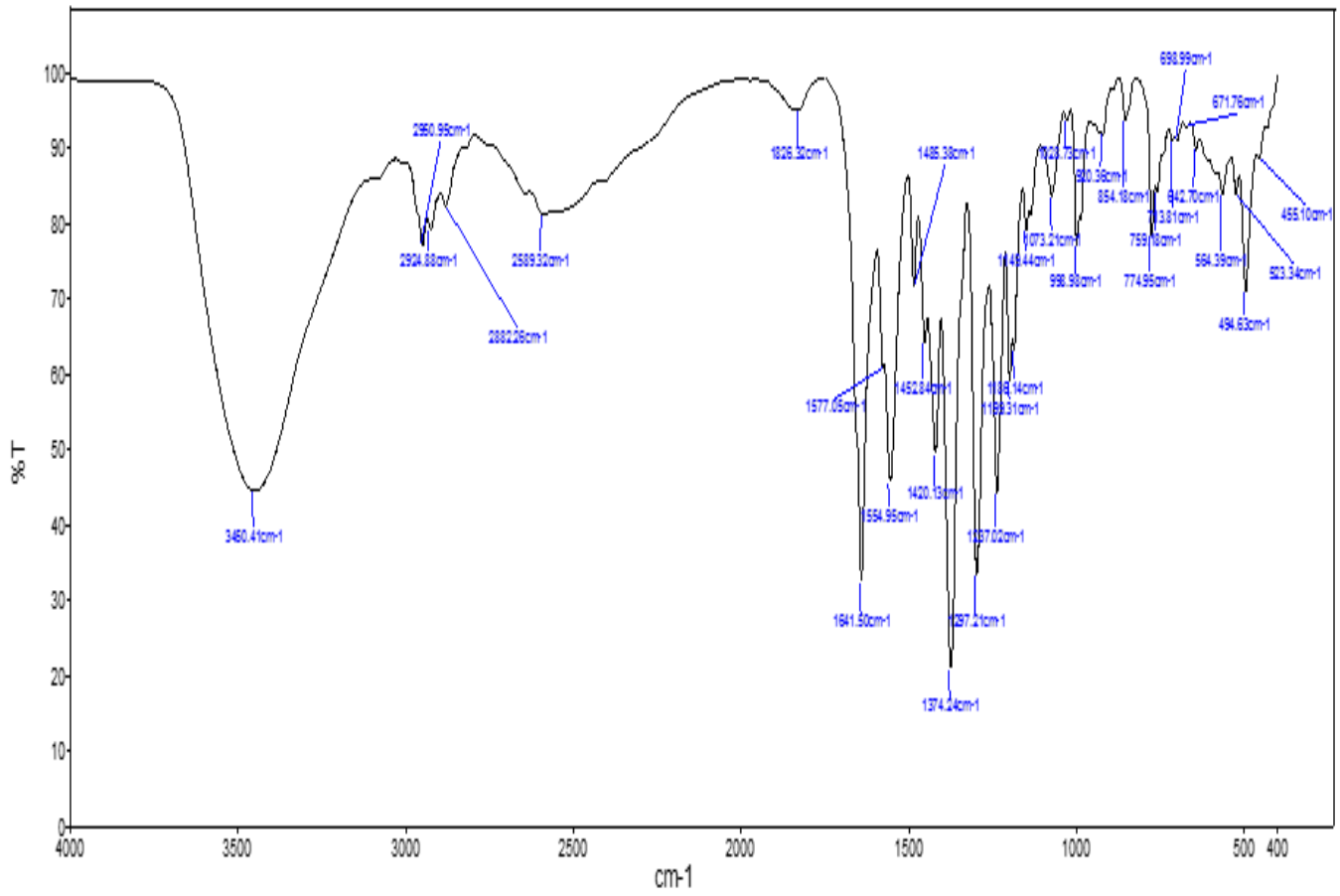


Fig. 43. Chromium complex (2d)-FT-IR spectra

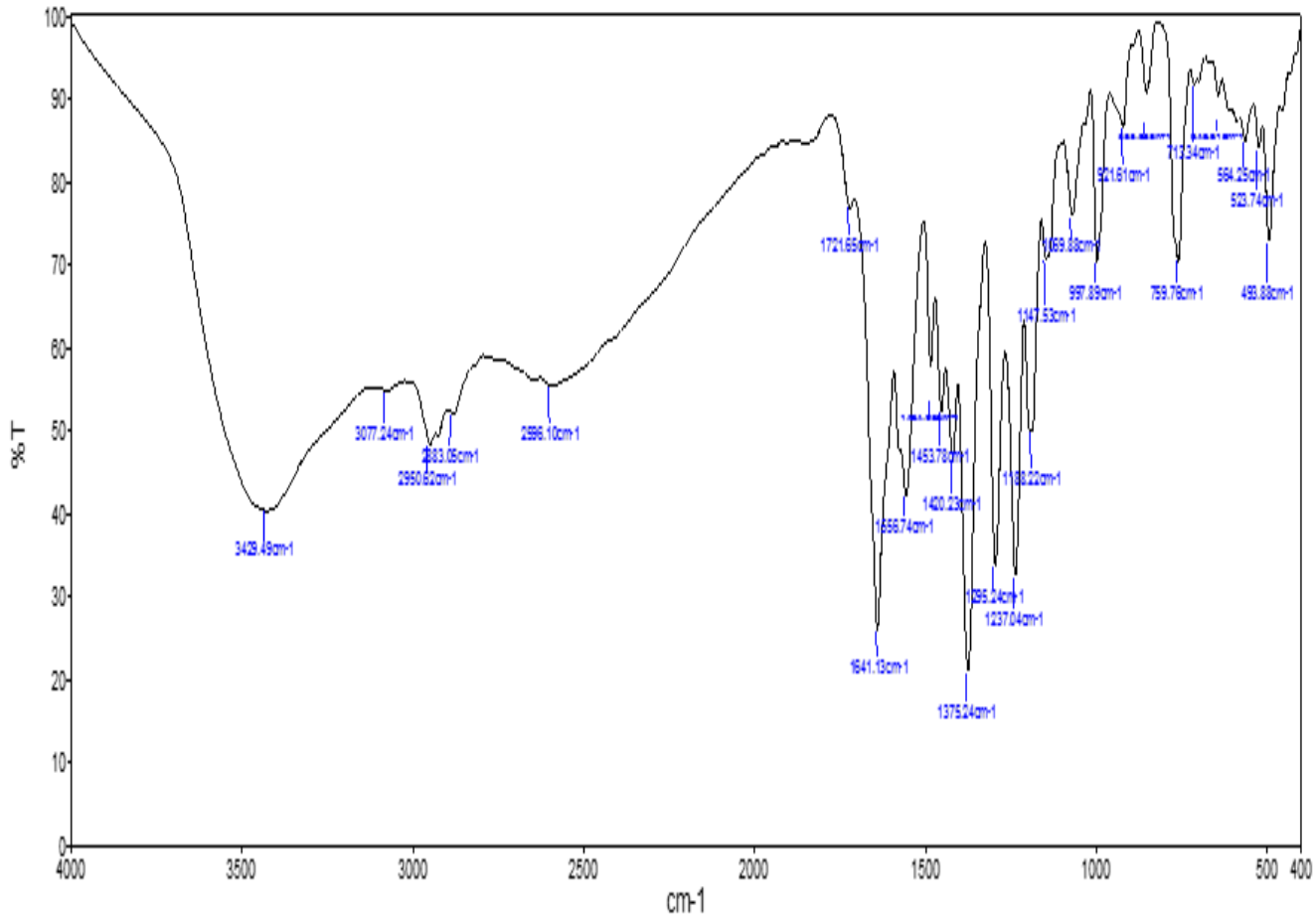


Fig. 44. Manganese complex (2e)-FT-IR spectra

5.2.7. UV-Visible Spectra

The ligand and complex UV-Visible spectra were measured in the region of 100-1100 nm. The UV spectra of ligand (**2**) primarily revealed two strong maximum bands at 375nm and 200nm, which correspond to the π →π* and n →π* transitions, correspondingly (Fig. 45). The Cu (II) complex being investigation has a wide band in the wavelength range of 262 nm, indicating octahedral geometry. Broad peaks at 262 nm and 290 nm were seen in the Ni (II) complex, confirming its octahedral

geometry. At 263nm, the location of bands detected for Cr (II) complex displays wide signals, indicating that it has an octahedral geometry. At 258 nm, the Fe (II) complex produced wide signals, confirming its octahedral geometry. The Mn (II) complex emitted wide signals at 262 nm, indicating that it is octahedral. Figure 46-50 shows the UV spectrums of metal complexes (**2a-2e**).

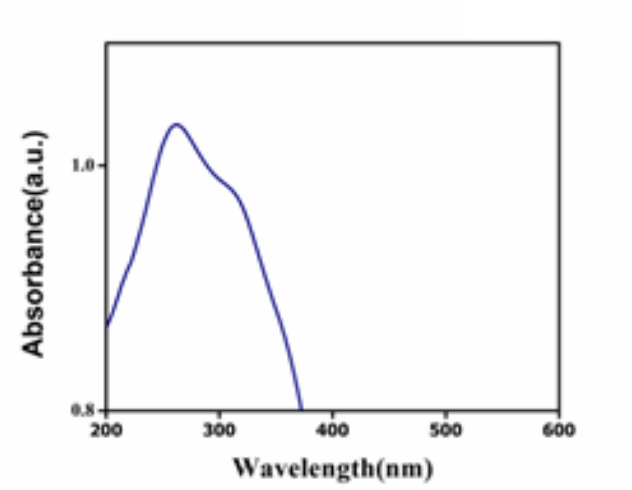


Fig. 45. Ligand 2 UV-Spectra

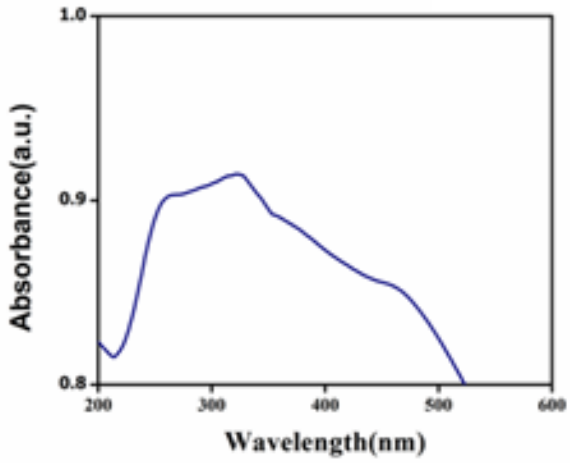


Fig. 46. Copper complex (2a) UV-Spectra

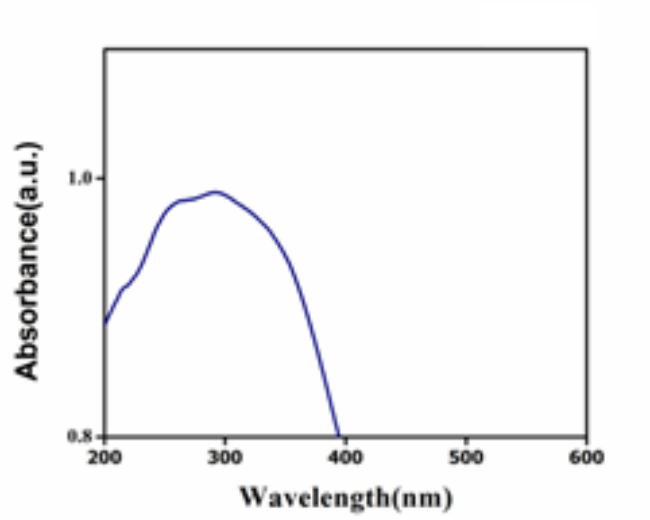


Fig. 47. Nickel complex (2b) UV-Spectra

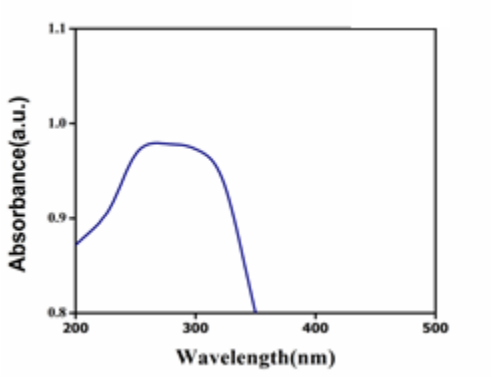


Fig. 48. Iron complex (2c) UV-Spectra

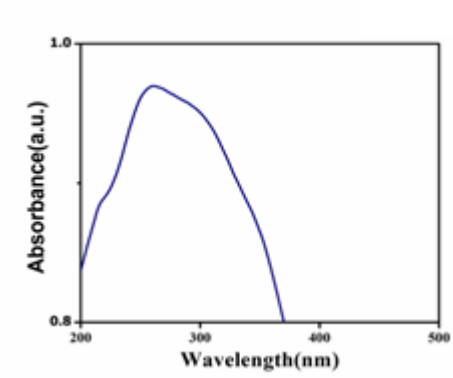


Fig. 49. Chromium complex (2d) UV-Spectra

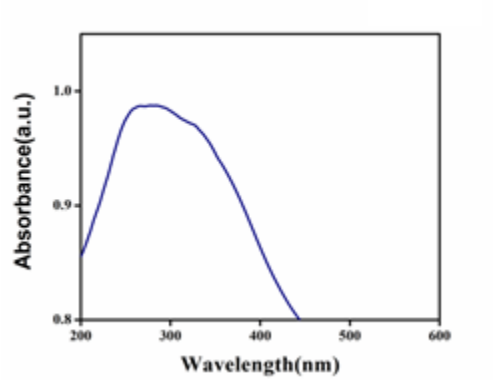


Fig. 50. Manganese complex (2e) UV-Spectra

5.2.8. EPR spectra

The type of metal ligand binding interactions and the arrangement of paired and unpaired electrons may be learned through EPR spectrum analysis. Cu (II) complexes have a unique character in coordination chemistry, with geometries such as tetrahedral, square planar, octahedral, and square pyramidal that may be distinguished by EPR spectroscopy. $g_{\parallel}$, $g^{\perp}$, gavg and G are EPR characteristics that indicate whether the compound is octahedral or tetrahedral. The following criterion confirms the existence of an unpaired electron in the dx^2-y^2 orbital: $g_{\parallel} > g^{\perp} > 2.0023$. For the copper complex, the measured $g_{\parallel}$ and $g^{\perp}$ values are 2.1462 and 2.0131, respectively. The ionic nature is shown by a $g_{\parallel}$ value more than 2.3, while the covalent nature is indicated by a $g_{\parallel}$ value less than 2.3. We can see that the g value (2.1462) is smaller than 2.3, indicating that the compound is covalent. According to Hathaway, G values less than four indicate a significant exchange contact amongst metal centers, whereas G values higher than four indicate a minimal

exchange interaction. The G value is 4.76 in this case, thus the exchange interaction is insignificant. The Cu (II) complex exhibits deformed octahedral geometry, according to the EPR characteristics. The EPR spectra of copper complex (**2a**) was shown in Fig. 51.

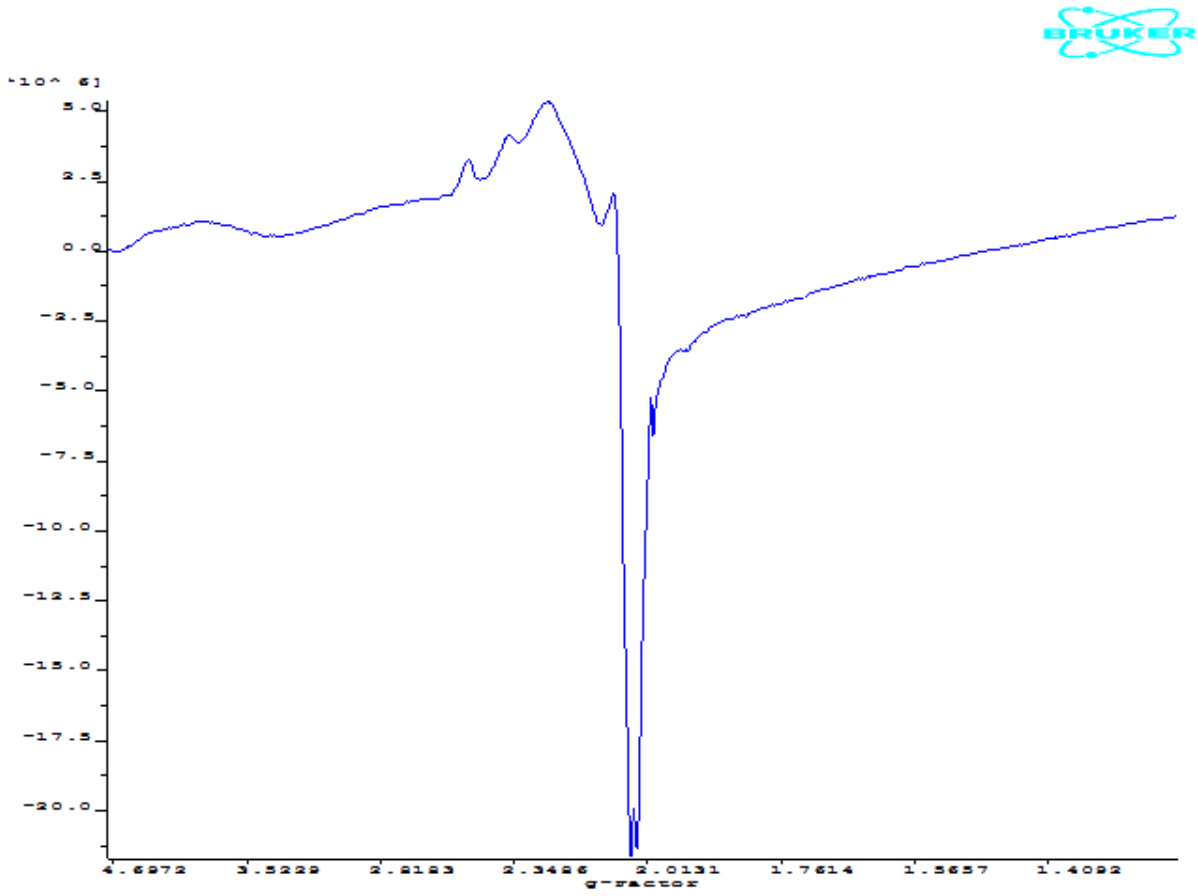
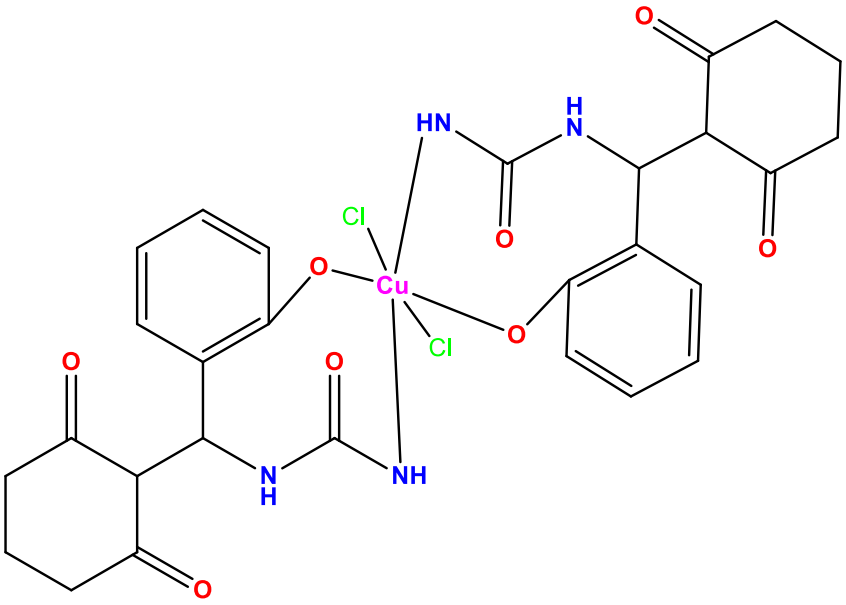


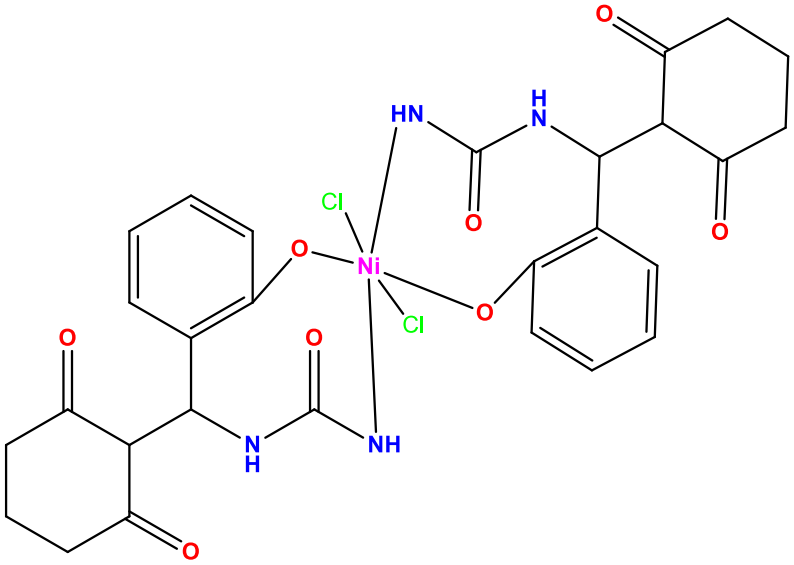
Fig. 51. Copper complex (2a) EPR spectra

5.2.9. Suggested Structure of the Complexes

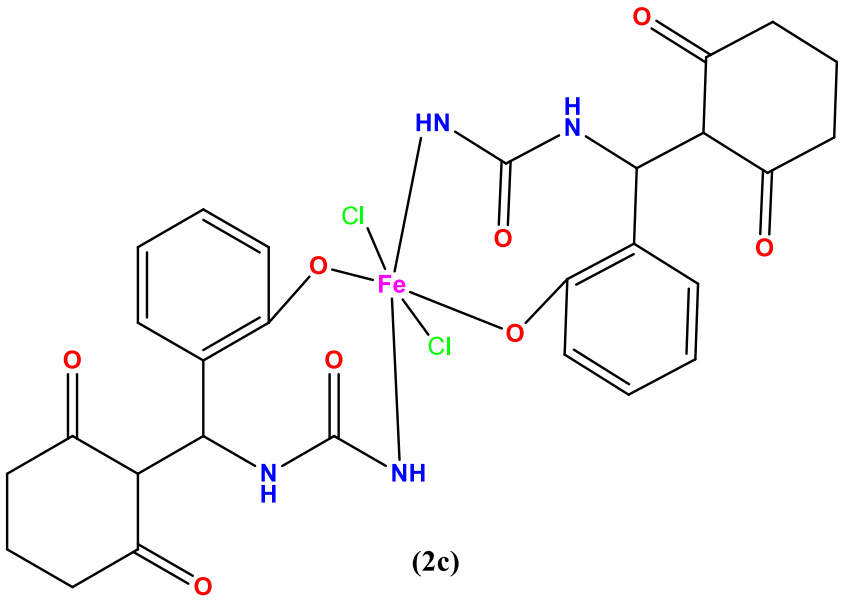
We recommend the following structure for the complexes (**2a-2e**) produced utilizing the Mannich base ligand (**2**) based on the preceding findings.



Structure of the Copper complex (2a) with ligand 2

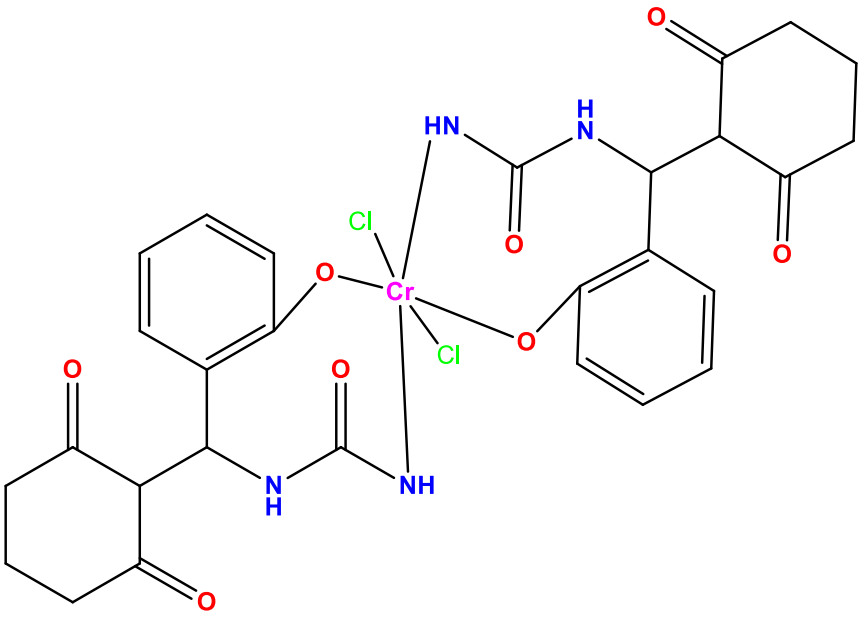


Structure of the Nickel complex (2b) with ligand 2

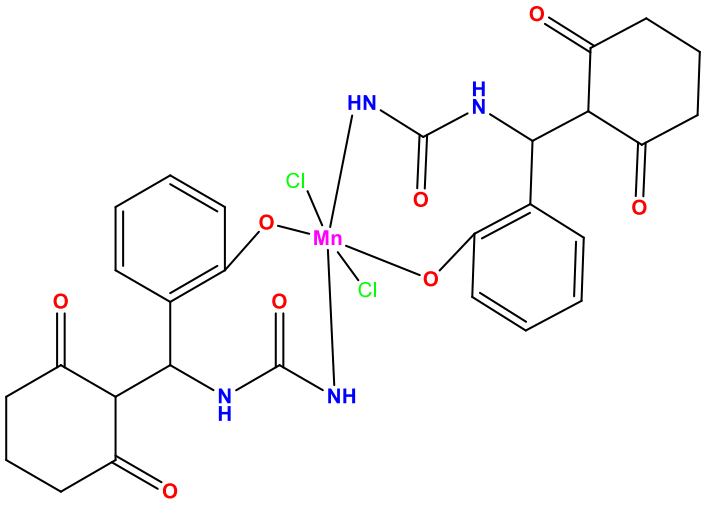


(2c)

Structure of the Iron complex (2c) with ligand 2



Structure of the Chromium complex (2d) with ligand 2



Structure of the Manganese complex (2e) with ligand 2

5.3. Metal complexes (3a-3e) with ligand (3)

5.3.1. Physical data

Table 9 shows the physical belongings of complexes (**3a-3e**) generated from the ligand (**3**).

Table 9. Physical belongings of complexes (3a-3e) and its ligand (3)

Compound	Color	Melting point (ºC)
Ligand (3)	Yellow	168
Copper complex (3a)	Blue	174
Nickel complex (3b)	Pale green	182
Iron complex (3c)	Brown	170
Chromium complex (3d)	Green	156
Manganese complex (3e)	white	160

5.3.2. Solubility

The solubility of the complexes (**3a-3e**) and ligand (**3**) in various solvents was investigated, and the findings are shown in Table 10. The ligand (**3**) as well as the metal complexes (**3a-3e**) were dissolved more readily in aprotic solvents than in protic solvents, according to solubility experiments.

Table 10. Solubility test results of complexes (3a-3e) and its ligand (3)

Compound	Water	Ethanol	Chloroform	DMSO
Ligand (3)	Insoluble	Insoluble	Sparingly soluble	Soluble
Copper complex (3a)	Insoluble	Insoluble	Insoluble	Soluble
Nickel complex (3b)	Insoluble	Insoluble	Insoluble	Soluble
Iron complex (3c)	Insoluble	Insoluble	Insoluble	Soluble
Chromium complex (3d)	Insoluble	Insoluble	Insoluble	Soluble
Manganese complex (3e)	Insoluble	Insoluble	Insoluble	Soluble

5.3.3. Conductivity and magnetic susceptibility measurements

Various solvents, including water, ethanol, chloroform, and DMSO, were used to test the solubility of the newly synthesized metal complexes. The Equiptronics digital conductivity meter (Model EQ-660) was used to determine

molar conductance in DMSO, with the cell constant calibrated using 0.1M KCl solutions. The electrical conductivity of a 10^{-3} M solutions of respective complexes (3a-3e) in DMSO was determined, revealing the complexes' neutral (non-electrolytic) character. The molar conductance of the mixed ligand complexes (**3a-3e**) of ligand (**3**) ranges from 16 to 24 $\Omega^{-1}mol^{-1}cm^2$. The chloride ions were shown to be coupled to metal ions via conductivity tests, suggesting that they function as ligands rather than ions. Constituents for the produced complexes were selected depending on the metal – ligand proportion (1:2) and the characteristics of the electrolytes as determined by conductance assays, which aids in understanding the structure of the complexes. The Conductance and magnetic properties of metal complexes (**3a-3e**) with ligand (**3**) were shown in Table 11.

Table 11. Conductance and magnetic properties of metal complexes (3a-3e) with ligand (3)

S. No	Compounds	Conductance ($\Omega^{-1}mol^{-1}cm^2$)	Magnetic Susceptibility (μ_{eff}. B.M)
1.	Copper complex (3a)	16	2.32
2.	Nickel complex (3b)	27	3.84
3.	Iron complex (3c)	25	5.76
4.	Chromium complex (3d)	20	4.72
5.	Manganese complex (3e)	24	5.16

5.3.4. NMR Spectra of ligand (3)

The hydrogens of the aromatic rings show a multiplet at 7.14-6.78 ppm in the ^{1}H NMR spectra of the Mannich base ligand (**3**) underneath investigation (Fig. 52). The methylene hydrogens linked to the salicylaldehyde and amine hydrogens of the thiourea show as a peak at 4.34 ppm, whereas the aromatic –OH occurs at 5.30 ppm. The ligand's creation is also determined by the change in a indication equivalent to the secondary amine $–NH_2$ hydrogen of as it was removed in the Mannich process. The carbons of the aromatic rings had peaks at 130.92-115.70 ppm in the ^{13}C NMR spectra of the Mannich base ligand (**3**) under investigation (Fig. 53). The presence of a peak at 61.14 ppm shows that the methylene carbon is linked to the salicylaldehyde and semicarbazide's amine hydrogens, respectively. Furthermore, the carbonyl carbon of the 1,3-cyclohexanedione component and the thiourea -C=S moiety are represented by the peaks at 208.34 and 182.01 ppm, respectively.

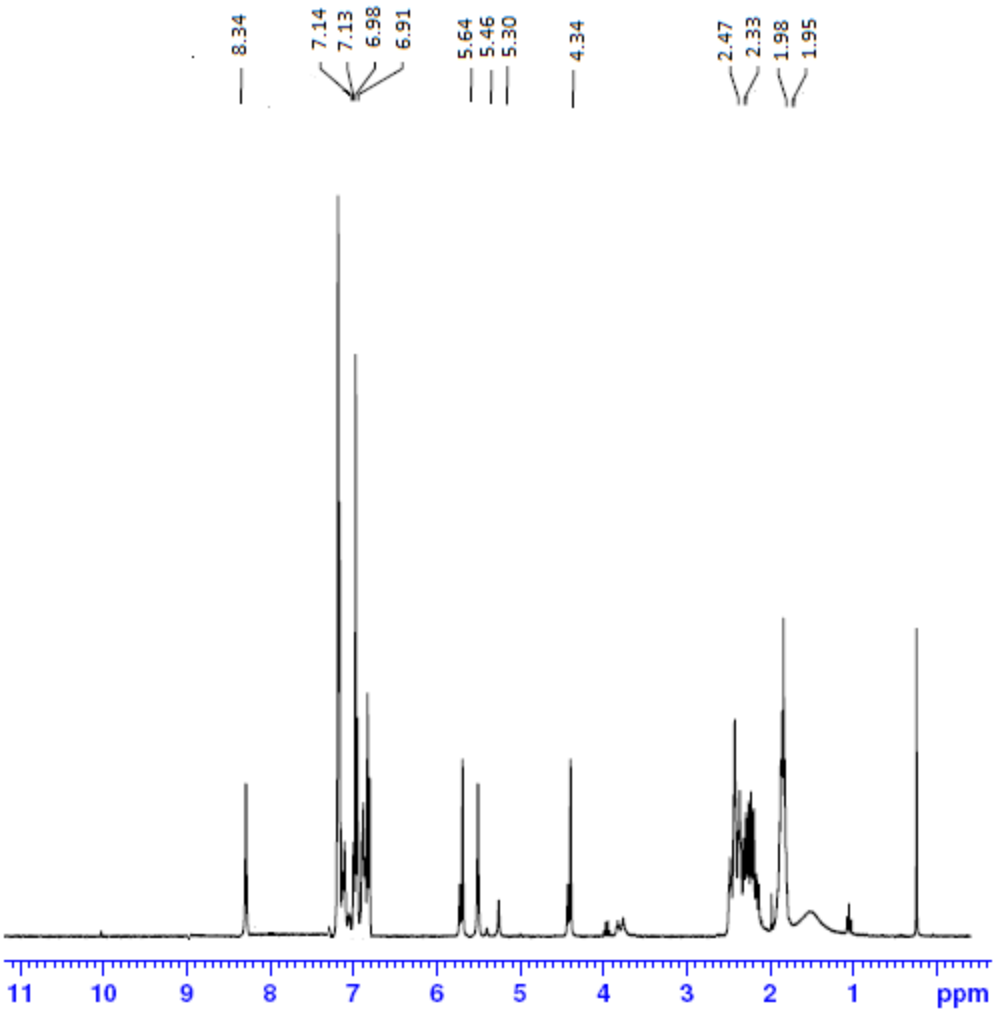


Fig. 52. Ligand (3)-^{1}H-NMR spectra

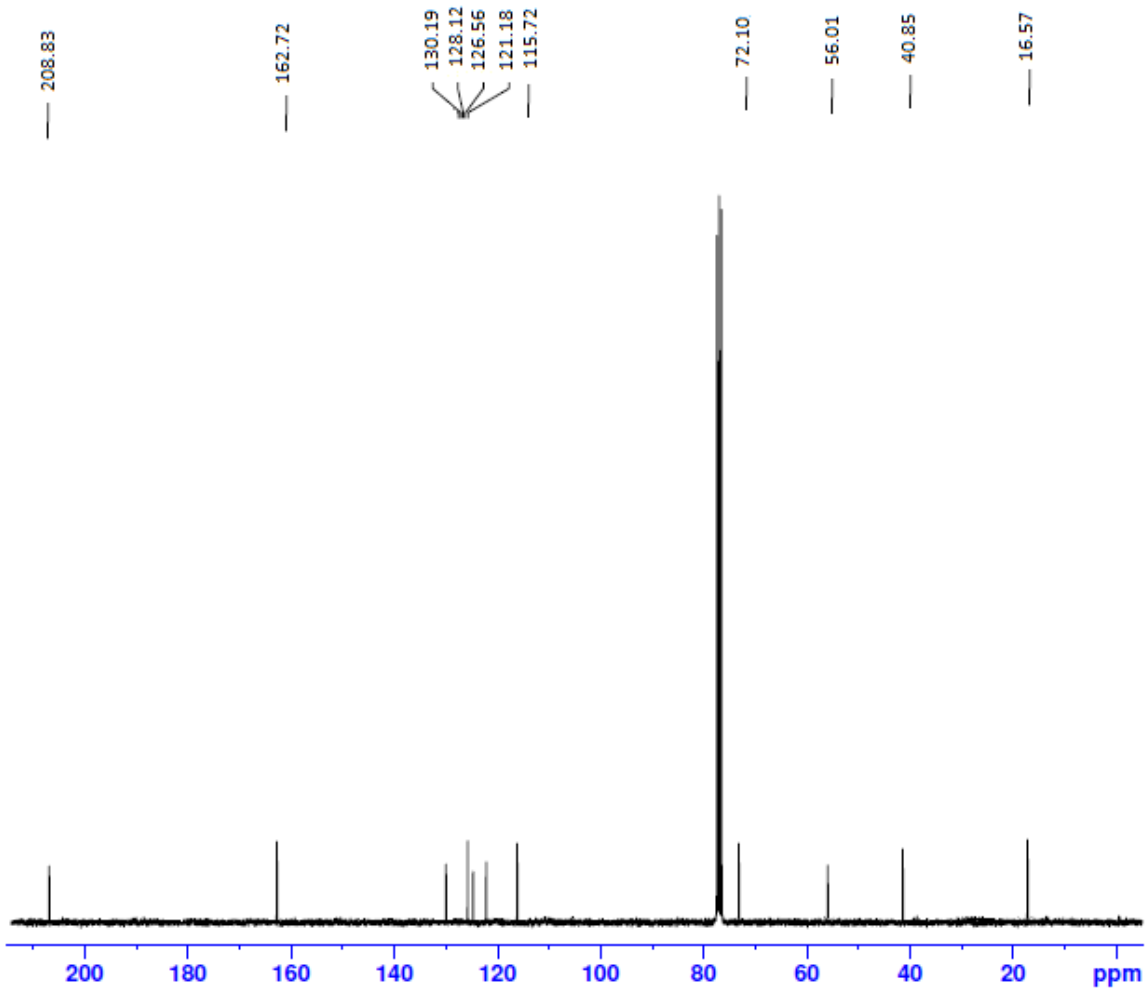


Fig. 53. Ligand (3)-^{13}C-NMR spectra

5.3.5. Mass Spectral studies of ligand (3)

The mass spectrum of the Mannich base ligand (**3**) below investigation (Fig. 54). The observed molecular weight of ligand (**3**) is 292.35 and that was confirmed by mass spectral studies at m/z 293.48. The molecular ion peak appeared at m/z 43.70. The other fragmentation peasks were m/z 257.69, 240.92, 206.87, 146.57, 120.19, 74.87, 64.63, 38.77 and 31.79 respectively.

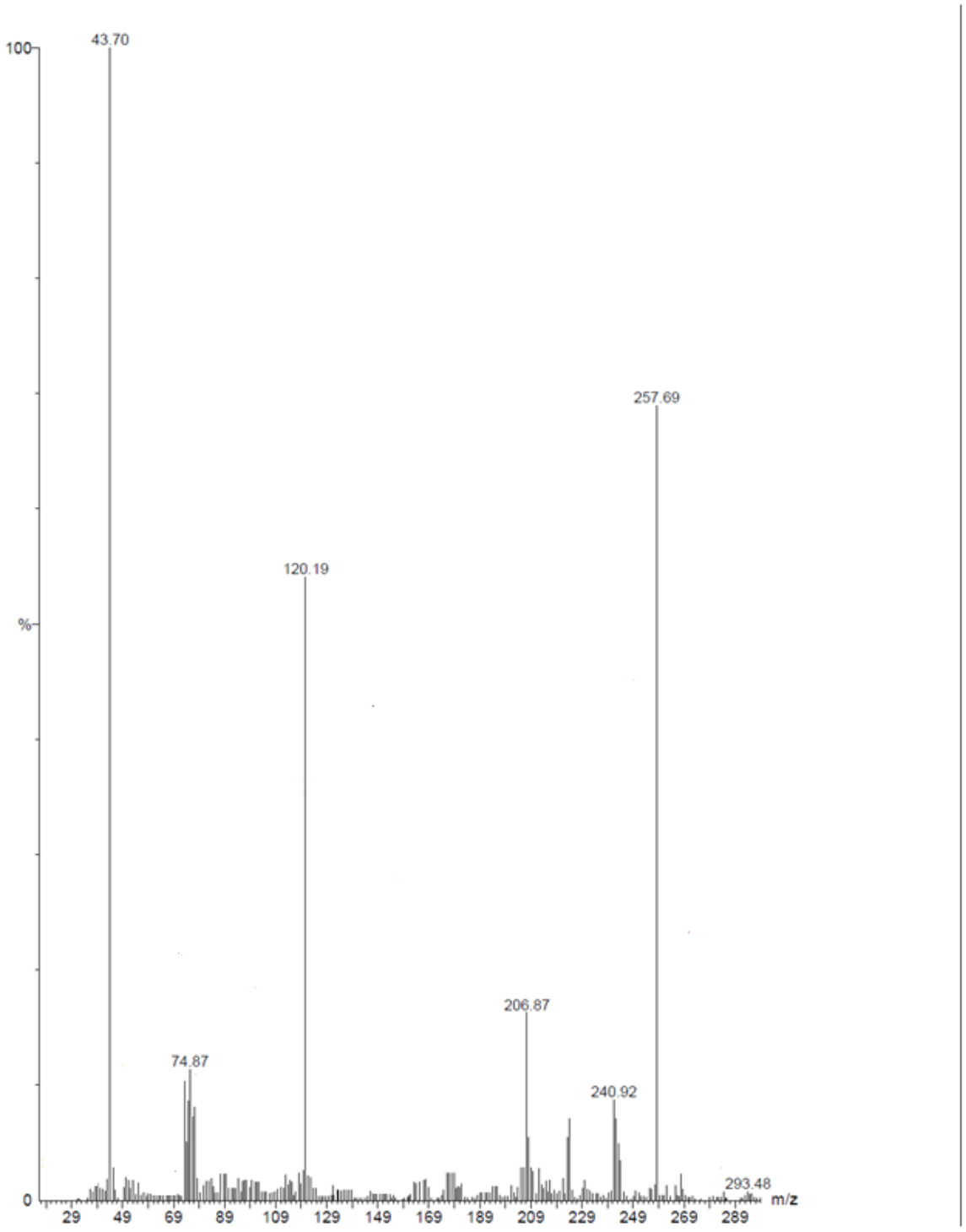
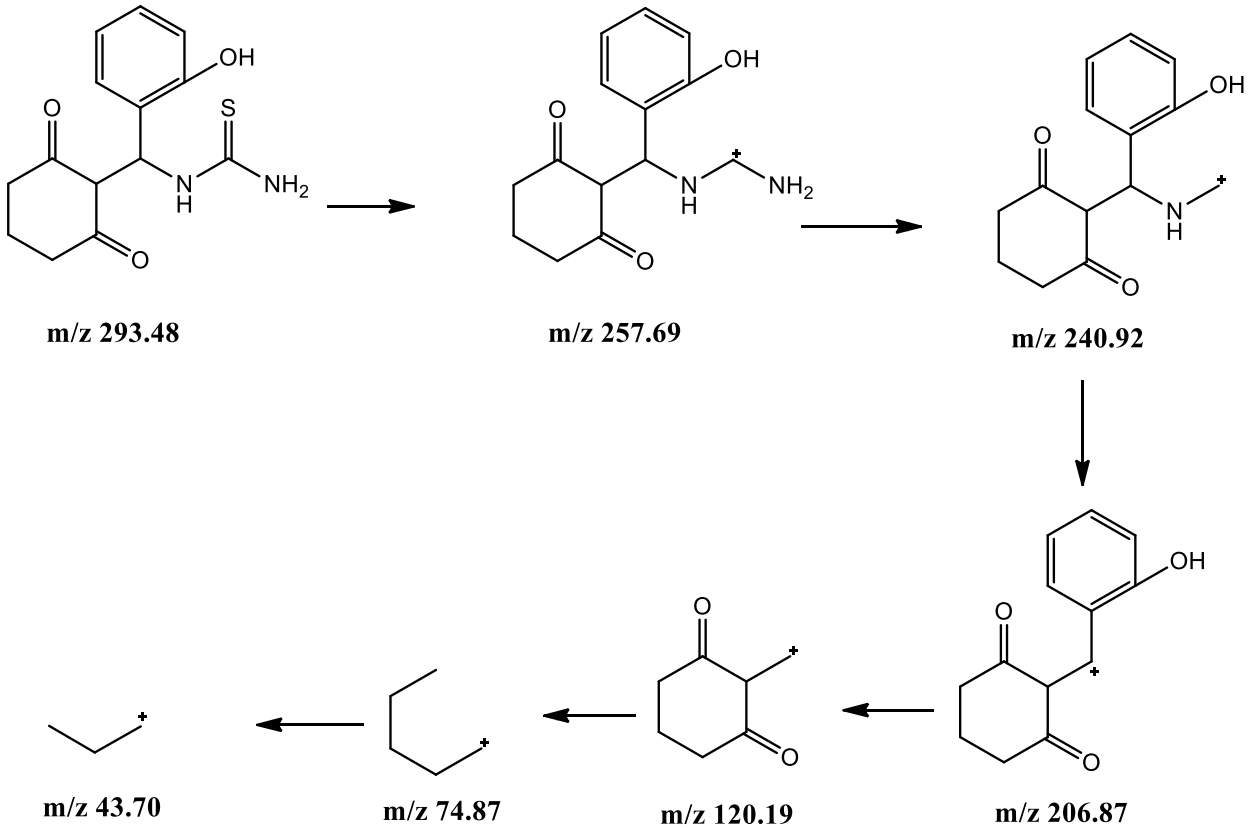


Fig. 54. Ligand (3)-Mass spectra



Mass spectral fragmentation pattern of Ligand 3.

5.3.6. IR Spectra

The existence of a strong band at 3399.42 and 3078.08 cm^{-1}, which would be attributable to the vO-H and N-H groups, is a significant finding in the ligand spectrum (Fig. 55). The bands attributable to O-H and N-H moved towards lower frequency in all the complexes (Fig. 56-60), suggesting that oxygen and nitrogen were engaged in coordination between metal ions. In copper complex (**3a**), the M-N bond is represented by the new peak at 853.08 cm^{-1}. The M-O bond is represented

by the new peak at 773.52 cm^{-1}. The new peak are appeared at 494.20 cm^{-1}, which corresponds to the M-Cl bond. The IR Spectral data of complexes (**3a-3e**) and the ligand (**3**) were displayed in Table 12.

Table 12. IR Spectral data of complexes (3a-3e) and the ligand (3)

Compound	IR stretching frequency (cm^{-1})				
	-OH	**-N-H**	**M-N**	**M-O**	**M-Cl**
Ligand (3)	3399.42	3078.08	-	-	-
Copper complex (3a)	3442.14	3075.89	853.08	773.52	494.20
Nickel complex (3b)	3440.89	3076.51	853.49	774.85	493.20
Iron complex (3c)	3420.14	3077.97	852.77	774.86	494.73
Chromium complex (3d)	3434.51	3077.65	853.82	773.93	493.21
Manganese complex (3e)	3436.54	2951.07	850.62	774.69	494.48

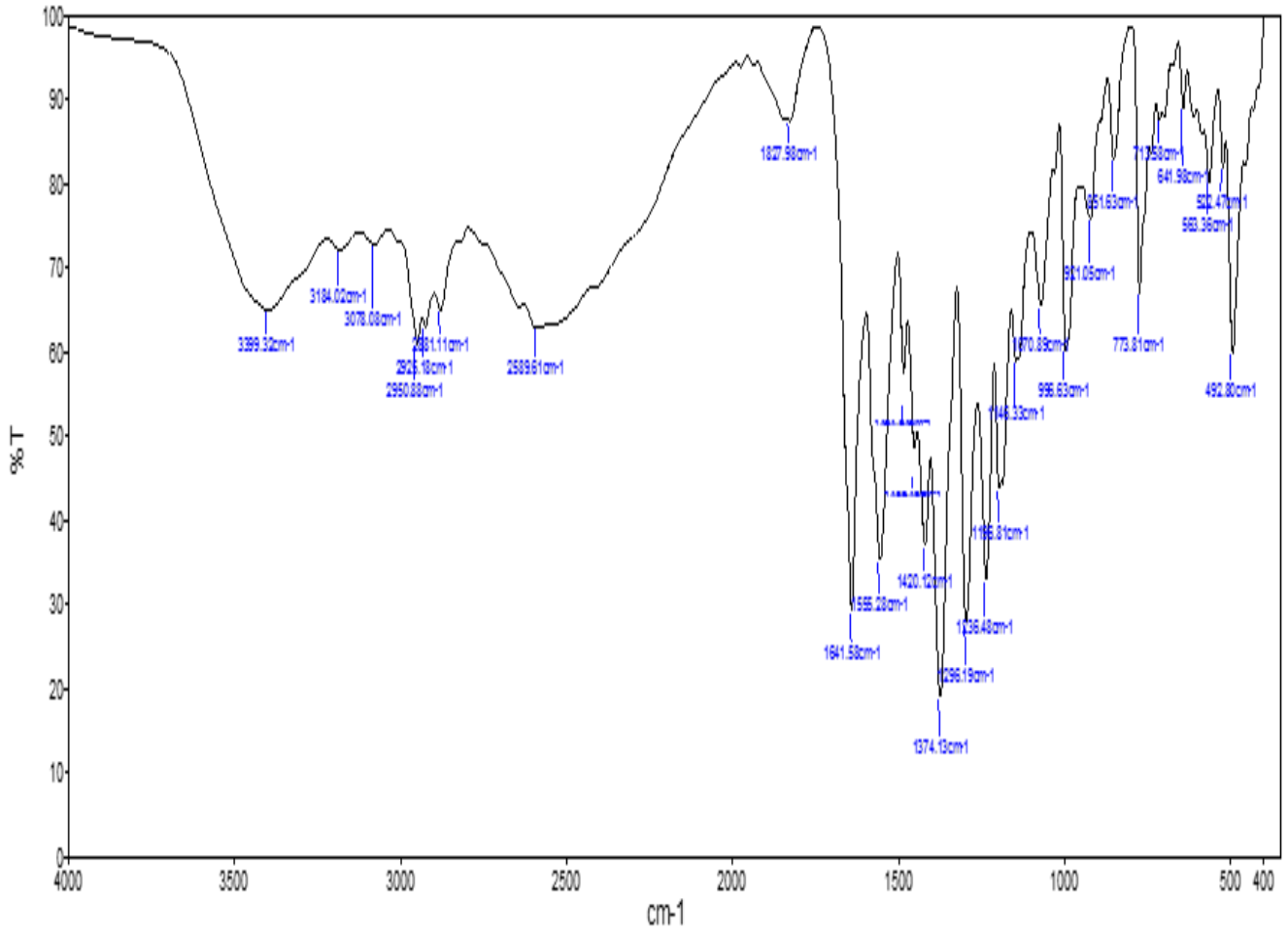


Fig. 55. Ligand (3)-FT-IR spectra

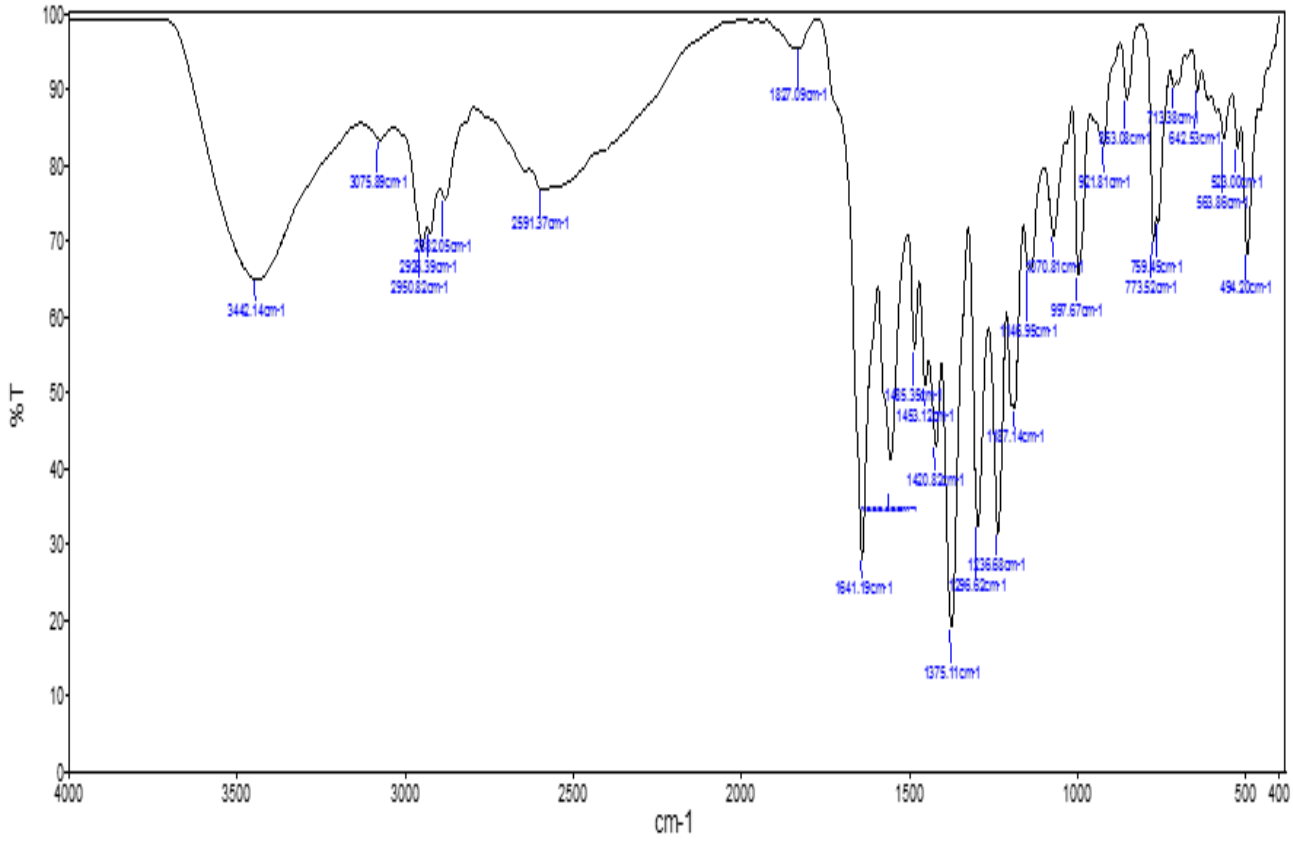


Fig. 56. Copper complex (3a)-FT-IR spectra

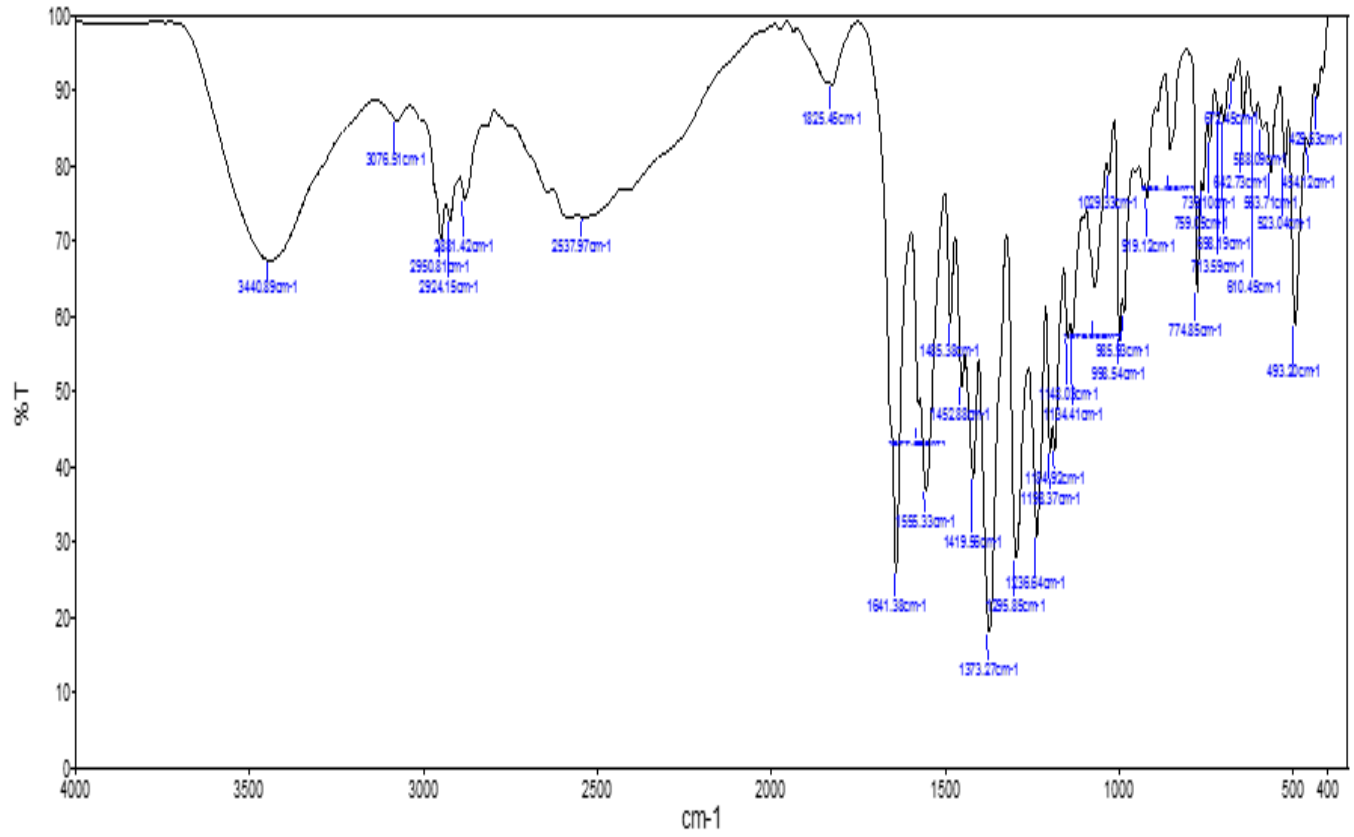


Fig. 57. Nickel complex (3b)-FT-IR spectra

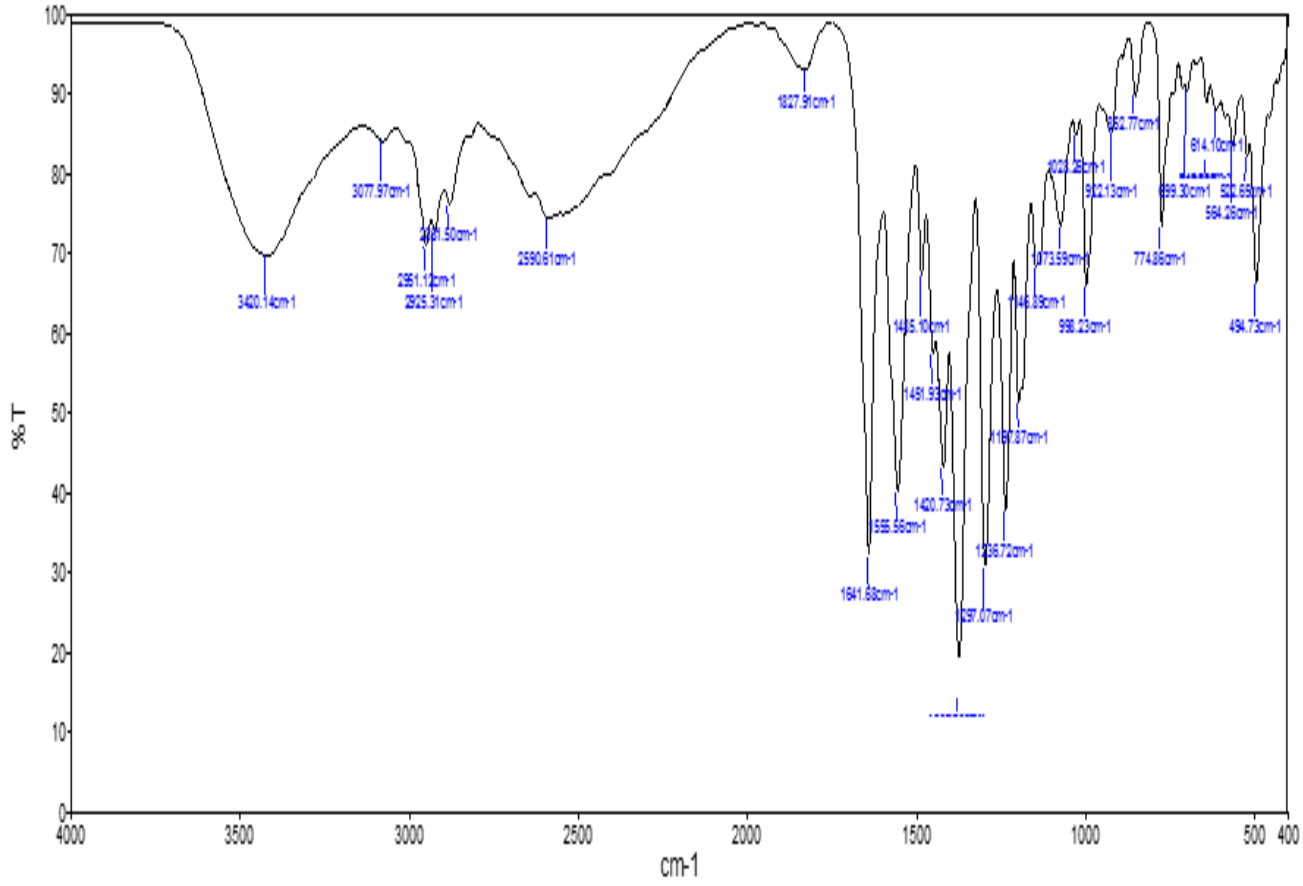


Fig. 58. Iron complex (3c)-FT-IR spectra

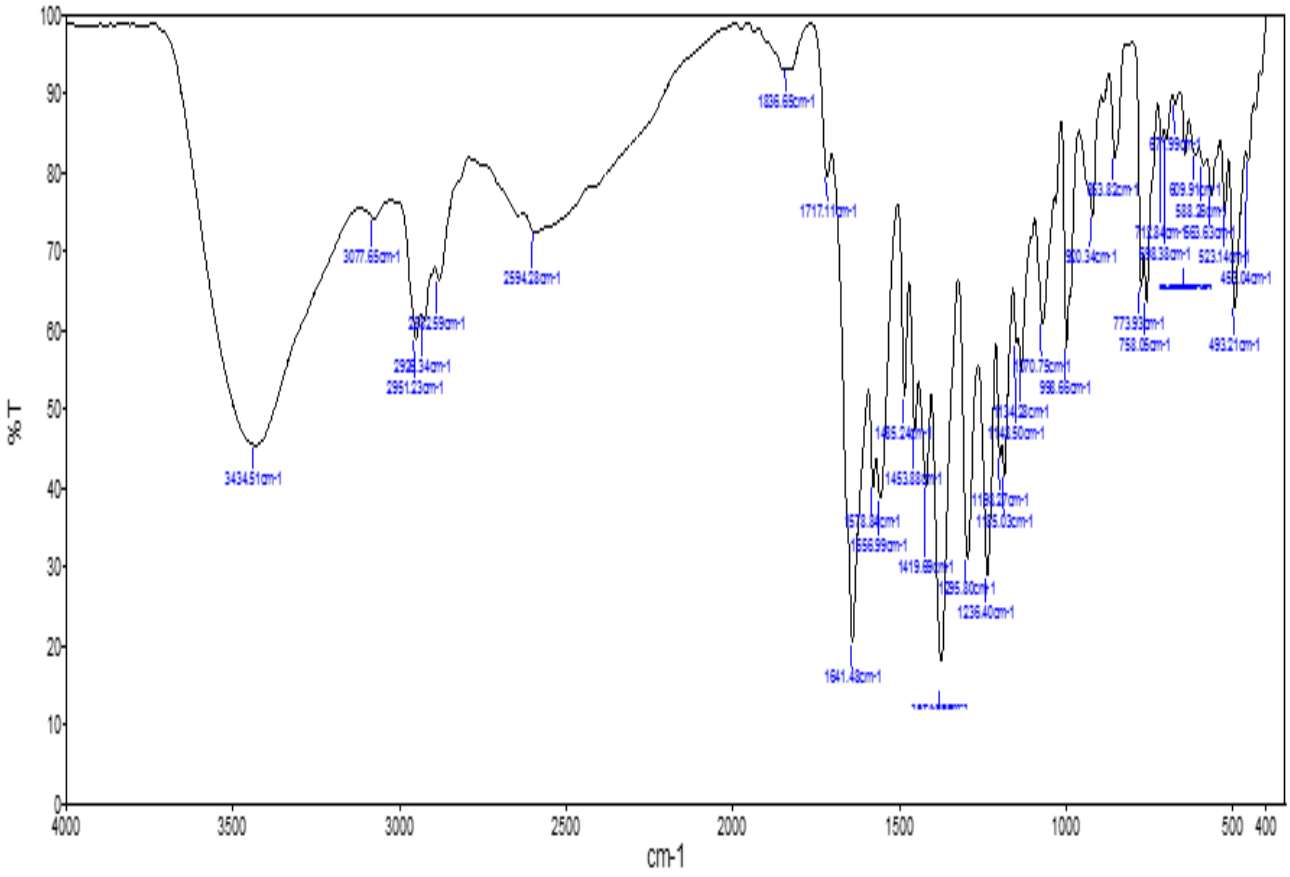


Fig. 59. Chromium complex (3d)-FT-IR spectra

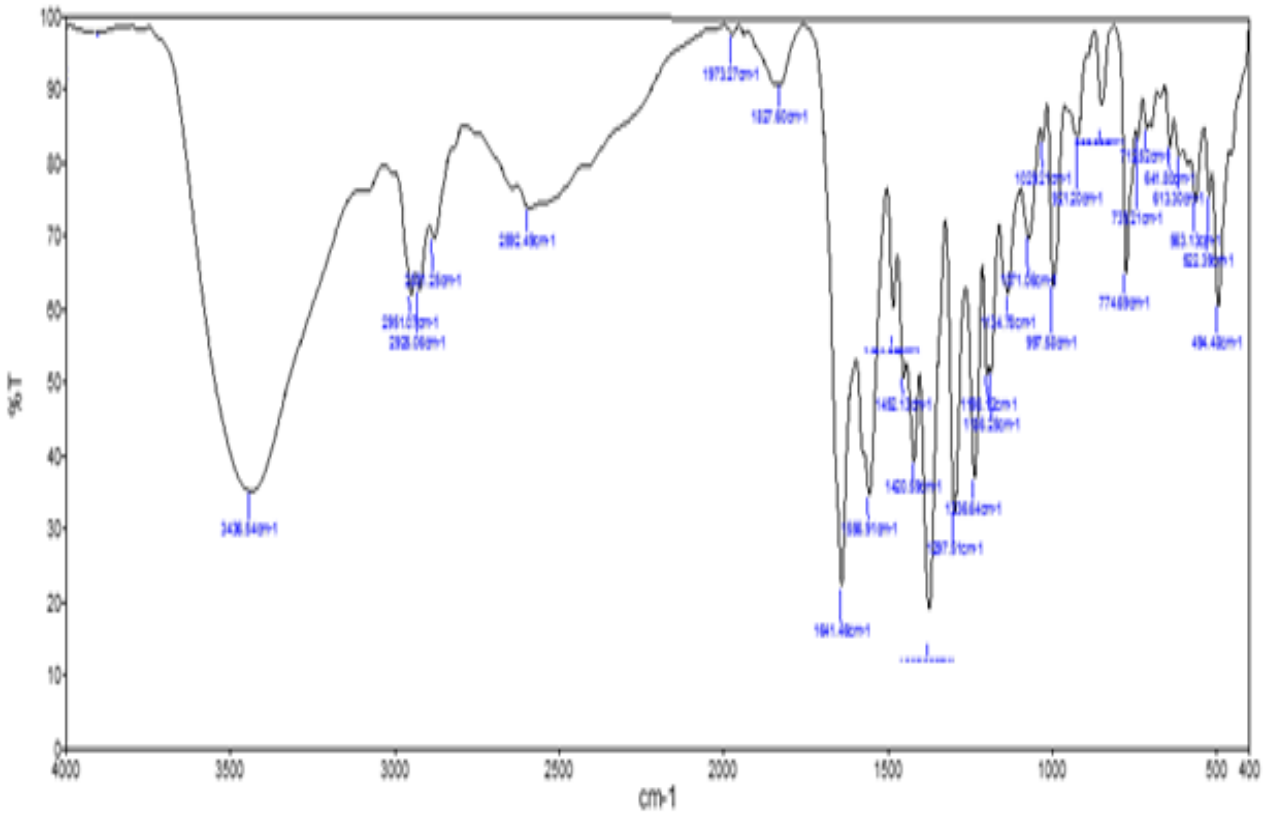


Fig. 60. Manganese complex (3e)-FT-IR spectra

5.3.7. UV-Visible Spectra

The ligand and complex UV-Visible spectra were measured in the region of 100-1100 nm. The UV spectra of ligand (**3**) primarily revealed two strong maximum bands at 375nm and 200nm, which correspond to the π →π* and n →π* transitions, correspondingly (Fig. 61). The Cu (II) complex in investigation has a wide band in the wavelength range of 262 nm, indicating octahedral geometry. Broad peaks at 262 nm and 290 nm were seen in the Ni (II) complex, confirming its octahedral

geometry. At 263nm, the location of bands detected for Cr (II) complex displays wide signals, indicating that it has an octahedral geometry. At 258 nm, the Fe (II) complex exhibited a wide signal, confirming its octahedral shape. The Mn (II) complex emitted wide signals at 262 nm, indicating that it is octahedral. Fig. 62-66 shows the UV spectrums of metal complexes (**3a-3e**).

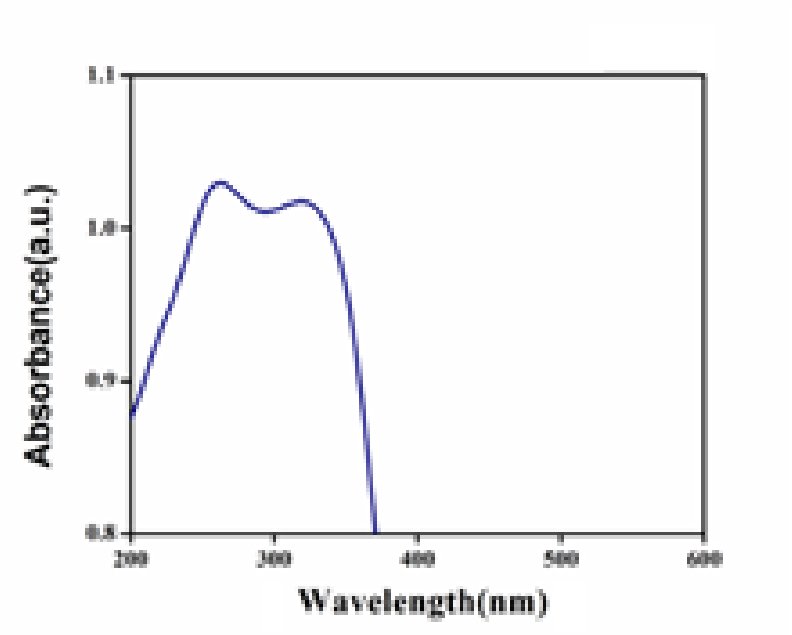


Fig. 61. Ligand 3 UV-Spectra

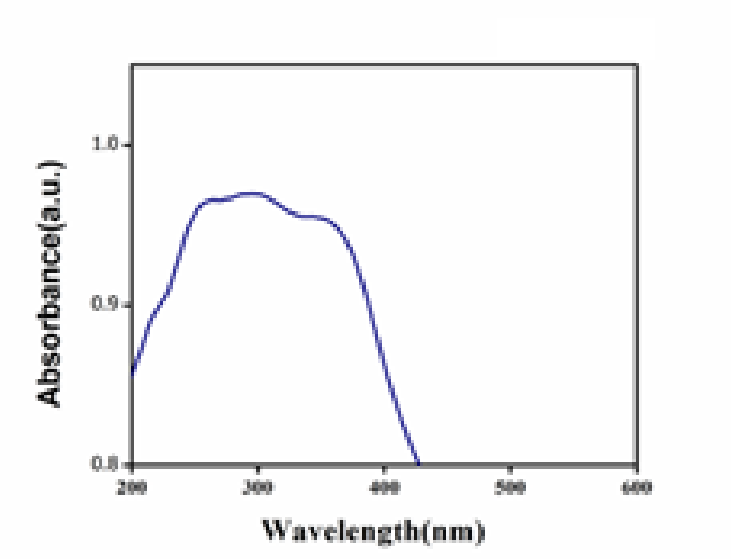


Fig. 62. Copper complex (3a) UV-Spectra

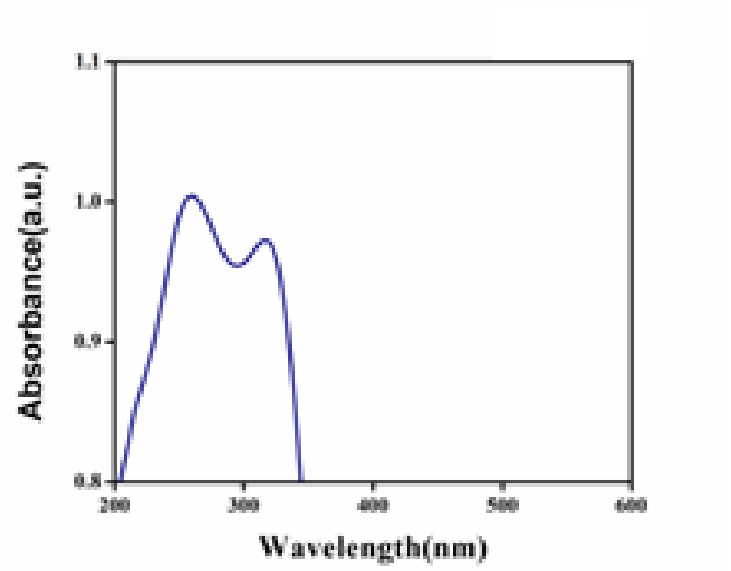


Fig. 63. Nickel complex (3b) UV-Spectra

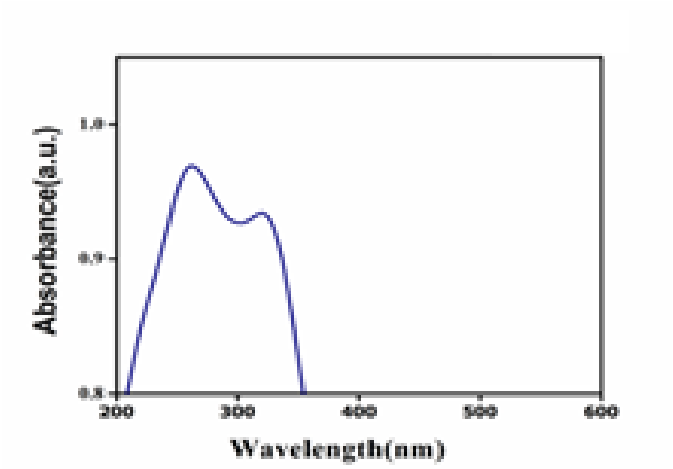


Fig. 64. Iron complex (3c) UV-Spectra

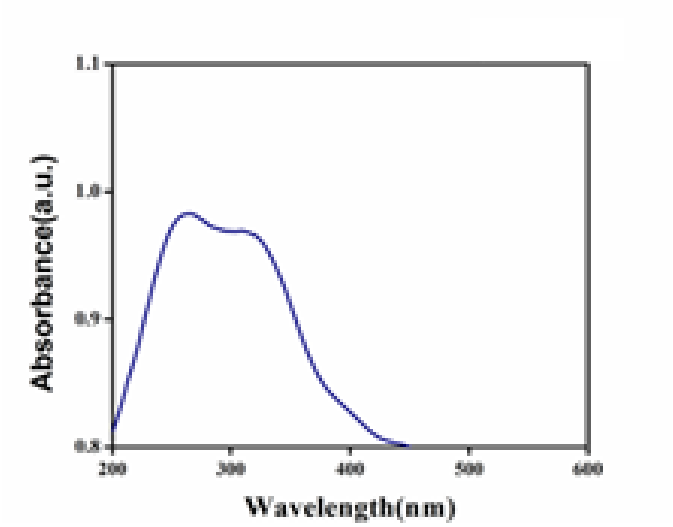


Fig. 65. Chromium complex (3d) UV-Spectra

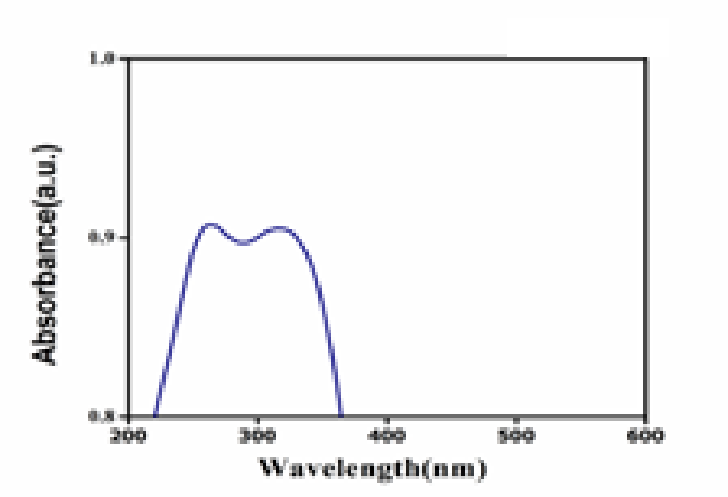


Fig. 66. Manganese complex (3e) UV-Spectra

5.3.8. EPR spectra

The type of metal ligand binding interactions and the arrangement of paired and unpaired electrons may be learned through EPR spectrum analysis. Cu (II) complexes have a unique character in coordination chemistry, with geometries such as tetrahedral, square planar, octahedral, and square pyramidal that may be distinguished by EPR spectra. $g_{\parallel}$, $g_{\perp}$, gavg and G are EPR characteristics that anticipate whether the compound is octahedral or tetrahedral. The following criterion confirms the existence of an unpaired electron in the dx^2-y^2 orbital: $g_{\parallel} > g_{\perp} > 2.0023$. For the copper complex, the measured $g_{\parallel}$ and $g_{\perp}$ values are 2.2645 and 2.0140, respectively. The ionic nature is shown by a g value more than 2.3, while the covalent nature is indicated by a $g_{\parallel}$ value less than 2.3. We can see that the g value (2.2645) is smaller than 2.3, indicating that the compound is covalent.

According to Hathaway, G values less than four indicate a significant exchange contact between metal centers, whereas G values higher than four indicate a minimal exchange interaction. The G value is 4.76 in this case, thus the exchange interaction is insignificant. The Cu (II) complex exhibits deformed octahedral geometry, according to the EPR characteristics. The EPR spectra of copper complex (**3a**) was shown in Fig. 67.

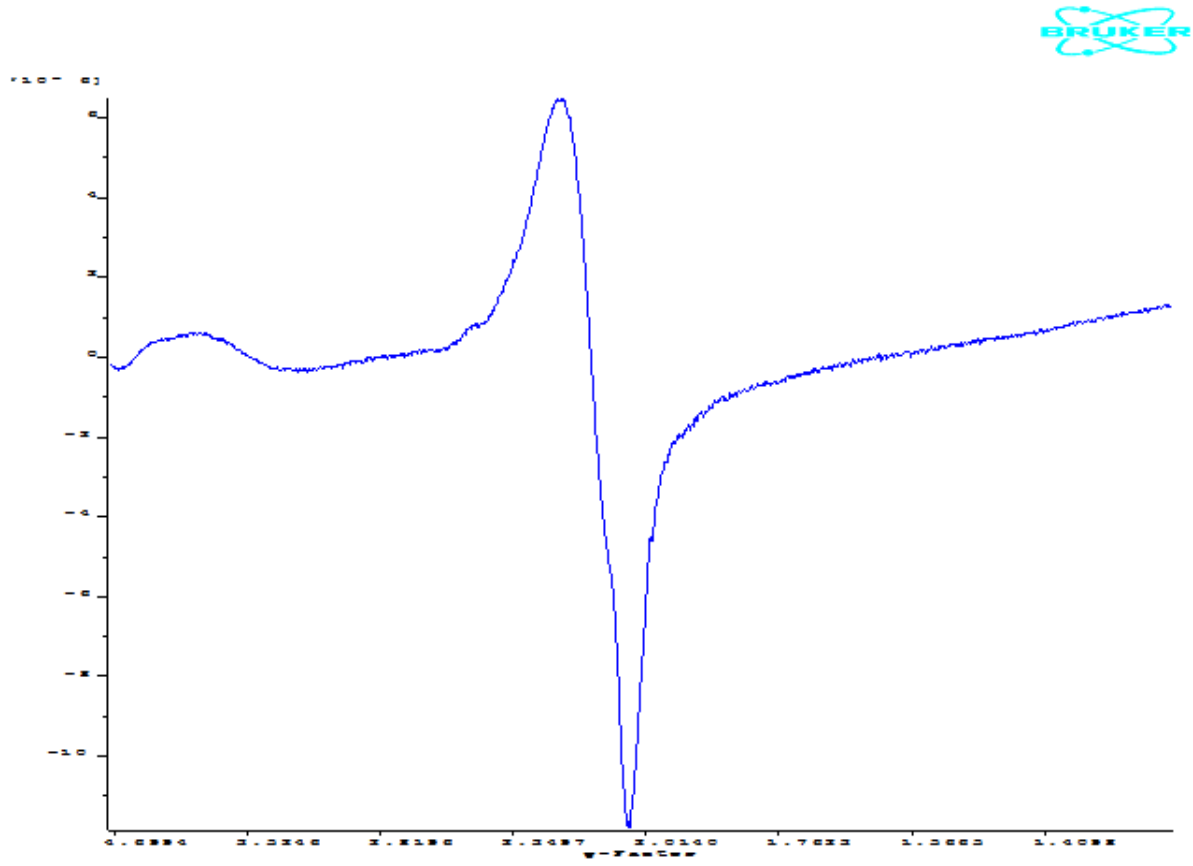
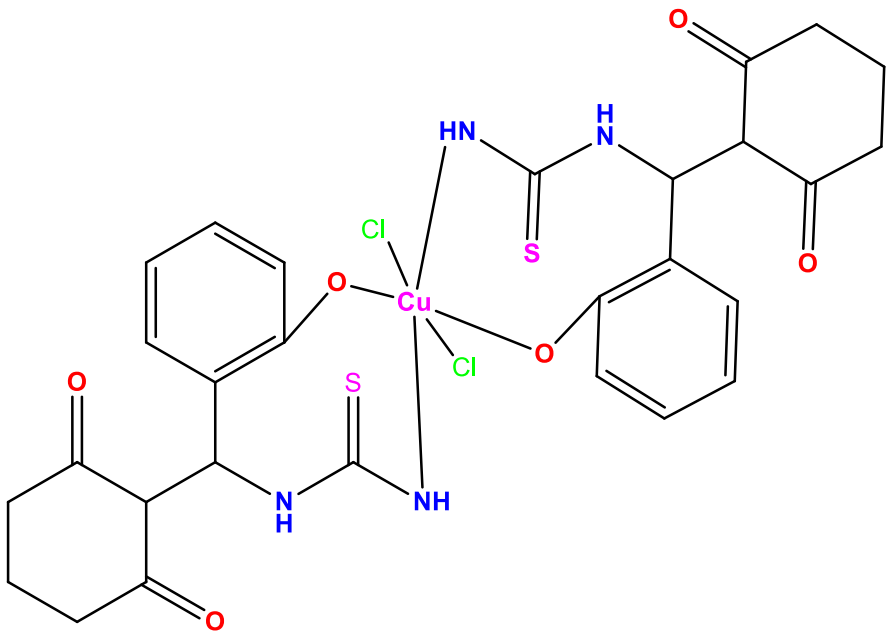


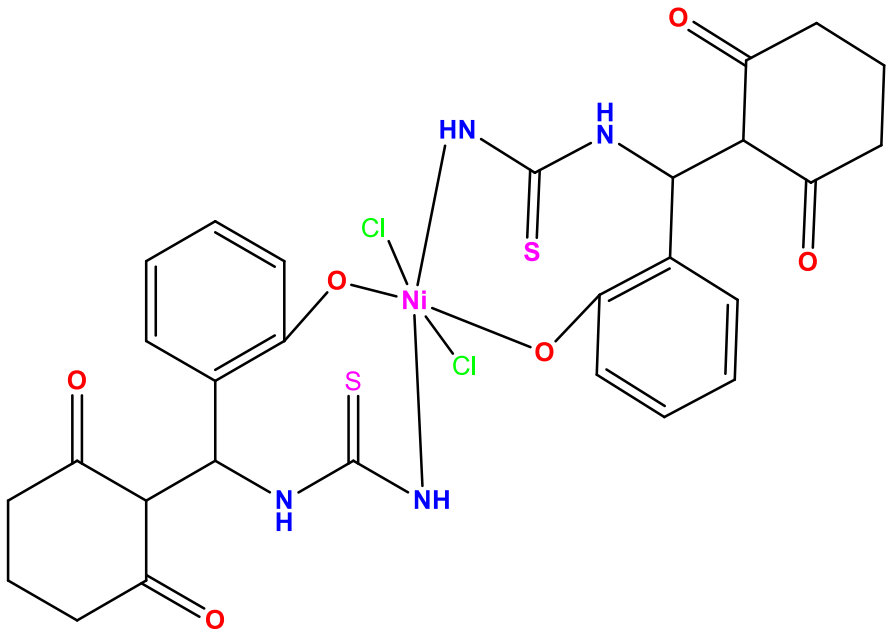
Fig. 67. Copper complex (3a) EPR spectra

5.3.9. Suggested Structure of the Complexes

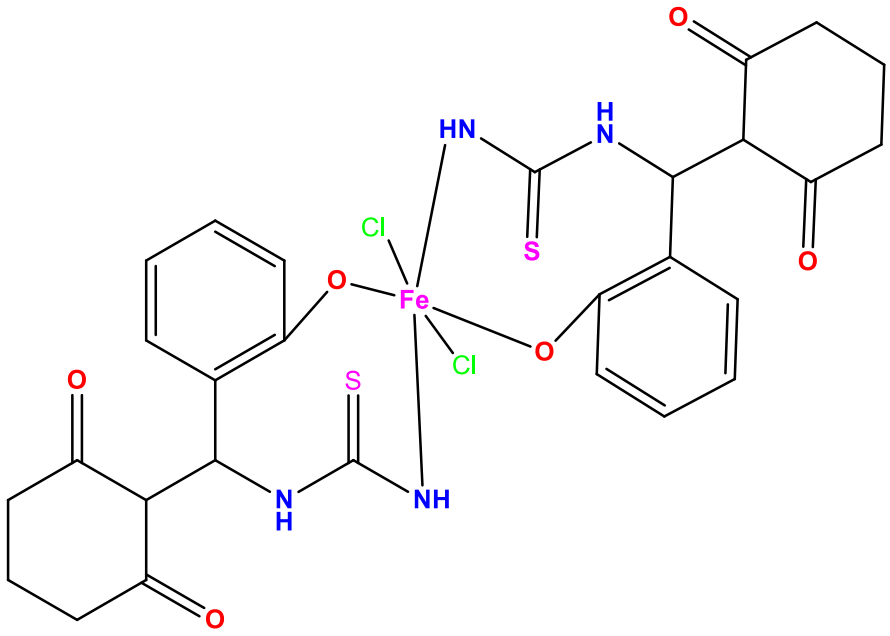
We propose the subsequent structure for complexes (**3a-3e**) produced with the Mannich base ligand (**3**) consistent with past findings.



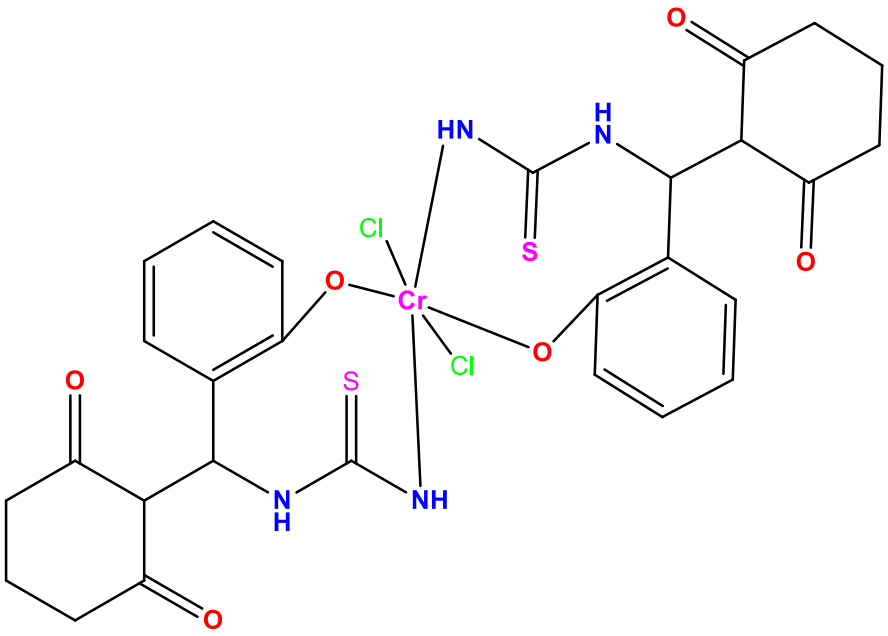
Structure of the Copper complex (3a) with ligand 3



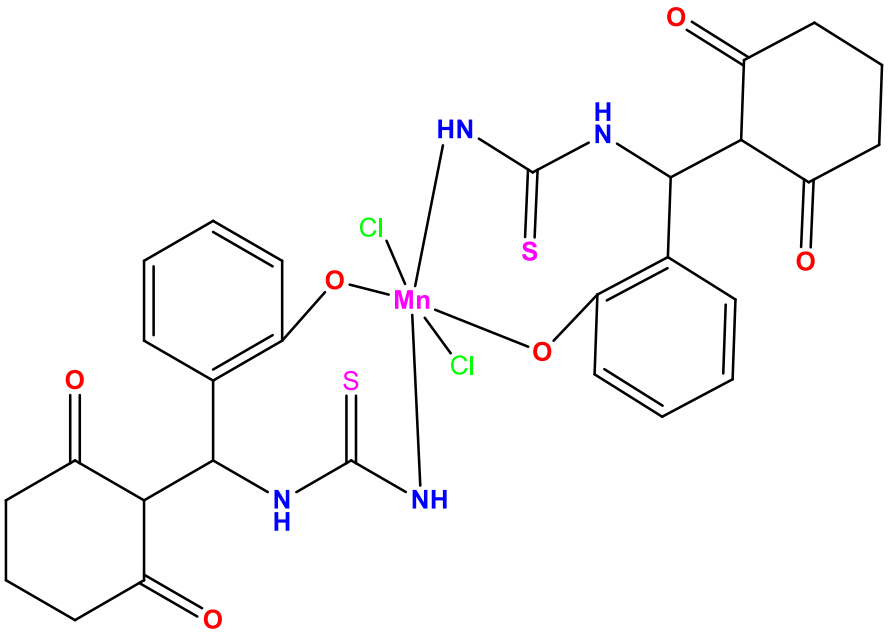
Structure of the Nickel complex (3b) with ligand 3



Structure of the Iron complex (3c) with ligand 3



Structure of the Chromium complex (3d) with ligand 3



Structure of the Manganese complex (3e) with ligand 3

5.4. Biological screening

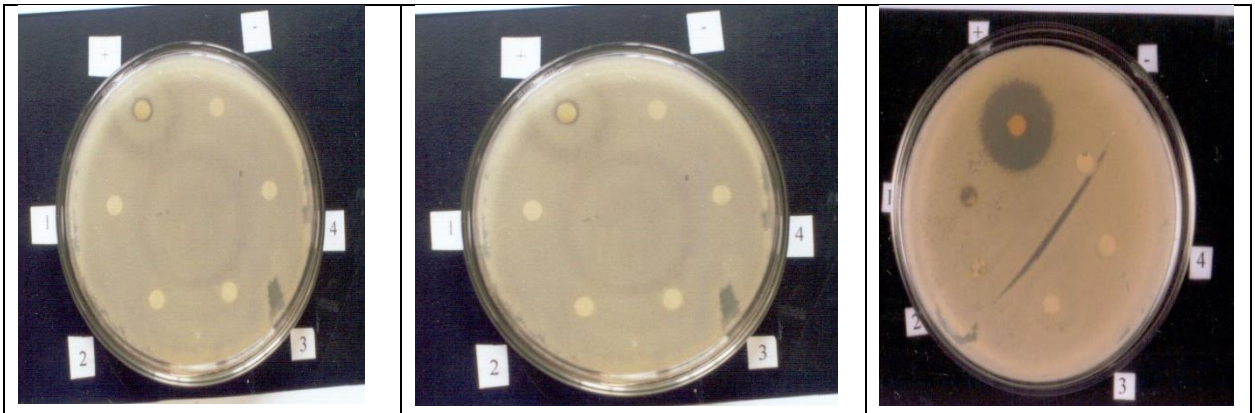
5.4.1. Antibacterial activity

The antibacterial activity of the synthesized ligand (**1-3**) and complexes (**1a-1e**), (**2a-2e**), (**3a-3e**) were tested. The ligands (**1-3**) had low activity compared to the corresponding complexes (**1a-1e**). The investigation was done in a controlled environment. In the (**1a-1e**), series, the complex **1a** was only highly active, with an MIC value of 2 µg/mL in *S.aureus*. Obviously, the chromium complex **1d** was more active against *K.neumoniae*, with MIC value of 4 µg/mL, than the control **Ciprofloxacin**, which had MIC value of 8 µg/mL. The iron complex **1c** was more active against *E.coli*, with MIC value of 4 µg/mL, than the control **Ciprofloxacin**, which had MIC value of 6 µg/mL. In comparison to complexes (**1a-1e**), complex **1a** (Cu II), complex **1c** (Fe II), and complex **1d** (Cr II), has exceptional activity. In the (**2a-2e**), series, the complex **2b** was only highly active, with an MIC of 2 µg/mL in *S. aureus*. Obviously, the copper complex **2a** was more active against *K. pneumoniae*, with MIC of 4 µg/mL, than the control **Ciprofloxacin**, which had MIC of 8 µg/mL. The manganese complex **2e** was more active against *E. coli*, with MIC of 4 µg/mL, than the control **Ciprofloxacin**, which had MIC of 6 µg/mL. In comparison to complexes (**2a-2e**), complex **2a** (Cu II), complex **2b** (Ni II), and complex **2e** (Mn II), has exceptional activity. In the (**3a-3e**), series, the complex **3c** was only highly active, with an MIC of 2 µg/mL in *S. aureus*. Obviously, the

chromium complex **3d** was more active against *K. pneumoniae*, with MIC of 4 µg/mL, than the control **Ciprofloxacin**, which had MIC of 8 µg/mL. The manganese complex **3e** was more active against *E. coli*, with MIC of 4 µg/mL, than the control **Ciprofloxacin**, which had MIC of 6 µg/mL. In comparison to complexes (**3a-3e**), complex **3c** (Fe II), complex **3d** (Cr II), and complex **3e** (Mn II), has exceptional activity. Table 13 summarizes the findings.

Table 13. Antibacterial activity of ligands (1-3) and complexes (1a-1e), (2a-2e), (3a-3e)

Compounds	Minimum inhibitory concentration (MIC) in µg/mL			
	S. aureus	***K. pneumaniae***	***E. coli***	***P. aeruginosa***
1	32	16	16	32
2	30	14	14	28
3	26	18	12	24
1a	2	12	10	8
1b	8	28	8	8
1c	10	14	4	4
1d	6	4	12	4
1e	12	16	8	4
2a	8	4	8	8
2b	2	10	10	4
2c	12	14	12	8
2d	6	12	8	4
2e	10	28	4	6
3a	4	8	6	4
3b	10	6	12	4
3c	2	12	10	6
3d	8	4	8	8
3e	10	28	4	6
Ciprofloxacin	4	8	6	2



Complex (1c)	Complex (2d)	Complex (3e)

Fig. 68. Antibacterial activity on *E. Coli*

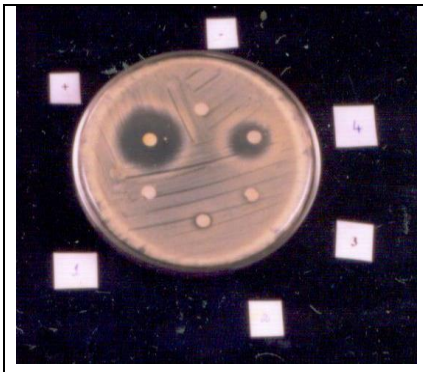
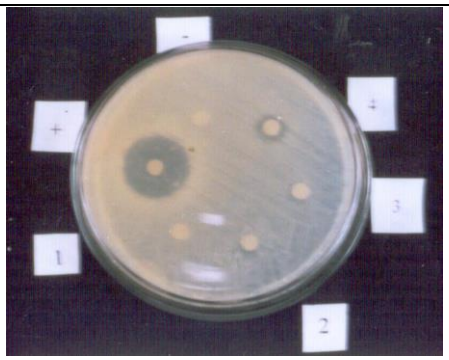
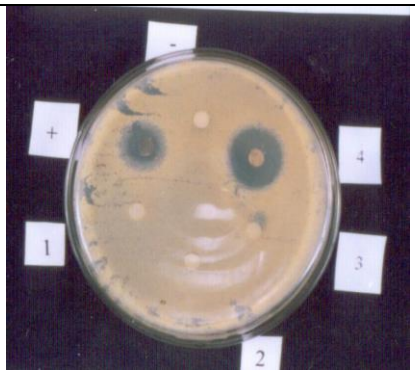
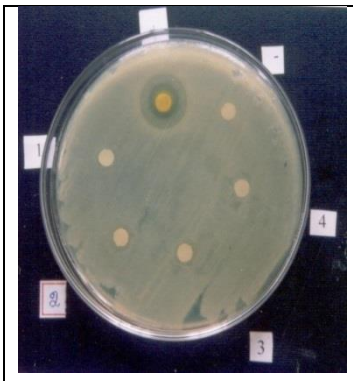
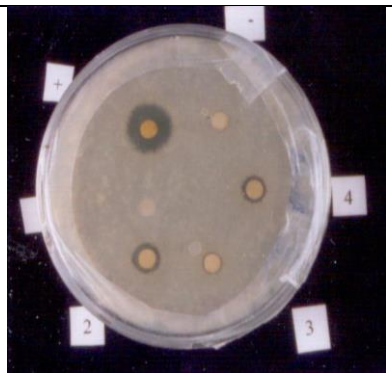
		
Complex (1a)	**Complex (2b)**	**Complex (3c)**

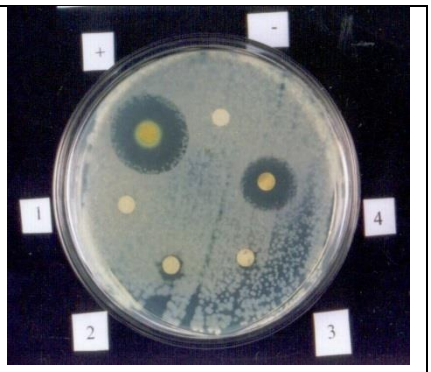
Fig. 69. Antibacterial activity on *S. aureus*



Complex (1d)



Complex (2a)



Complex (2d)

Fig. 70. Antibacterial activity on *K. pneumaniae*

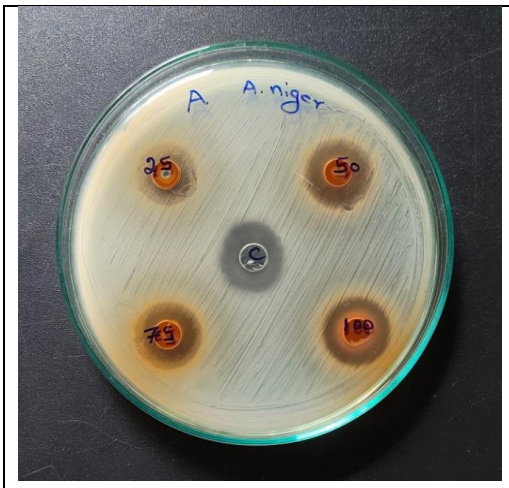
5.4.2. Antifungal activity

The antifungal activity of the synthesised ligands (**1-3**) and their complexes (**1a-1e**), (**2a-2e**), and (**3a-3e**) was investigated. In comparison to the comparable complexes, the ligands (**1-3**) displayed poor activity (**1a-1e**). The complex **1a** in the (**1a-1e**) sequence was only moderately active in *C. albicans*, with a MIC of 6 g/mL. The chromium complex **1b**, with a MIC of 3 g/mL, was clearly more active against *C. neoformans* than the standard **Amphotericin B**, which had a MIC of 4 g/mL. With a MIC of 6 g/mL, the iron complex **1c** was more effective towards A. niger than the standard **Amphotericin B**, which had a MIC of 12 g/mL. Complex **1a** (Cu II), complex **1b** (Ni II), and complex **1c** (Fe II) have extraordinary activity when compared to complexes (**1a-1e**). The complex **2b** was only moderately active in the (**2a-2e**) group, with a MIC of 6g/mL in *C. albicans*. With a MIC of 2 g/mL, the chromium complex **2d** was clearly more active towards **C. neoformans** than the standard **Amphotericin B**, which had a MIC of 4 g/mL. The copper complex **2a** was more active towards *A. niger*, with MIC of 8 g/mL, than the standard **Amphotericin B**, which had MIC of 12 g/mL. Complex **2a** (Cu II), complex **2b** (Ni II), **2c** (Fe II), and complex **2d** (Cr II) have extraordinary activity when compared to complexes (**2a-2e**). The complex **3e** of the (**3a-3e**) group was only reasonably active in *C. albicans*, with a MIC of 4 g/mL. With a MIC of 3 g/mL, the iron complex **3c** was clearly more potent towards *C. neoformans* than the standard **Amphotericin B**,

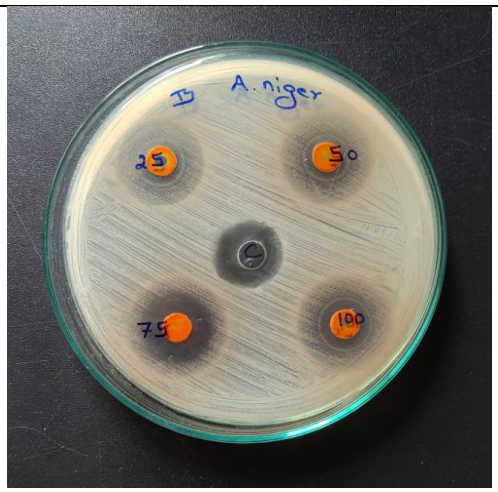
which had a MIC of 4 g/mL. With a MIC of 6 g/mL, the chromium complex **3d** was more effective towards *M. audouinii* than the standard **Amphotericin B**, which had a MIC of 10 g/mL. With a MIC of 8 g/mL, the nickel complex **3b** was more efficient towards A. niger than the standard **Amphotericin B**, which had a MIC of 12 g/mL. Complex **3e** (Mn II), complex **3c** (Fe II), complex **3d** (Cr II), and complex **3b** (Ni II) have extraordinary activity when compared to complexes (**3a-3e**). The results are summarised in Table 14.

Table 14. Antifungal activity of ligands (1-3) and complexes (1a-1e), (2a-2e), (3a-3e)

Compounds	Minimum inhibitory concentration (MIC) in µg/mL			
	C. albicans	*C. neoformans*	*M. audouinii*	*A. niger*
1	18	24	18	14
2	14	26	16	10
3	16	20	14	12
1a	06	-	12	16
1b	12	03	10	24
1c	-	16	-	06
1d	12	11	-	14
1e	14	11	08	15
2a	10	09	12	08
2b	06	-	16	12
2c	17	10	06	10
2d	-	02	18	14
2e	15	12	16	12
3a	11	15	11	-
3b	13	11	10	08
3c	19	03	14	14
3d	11	14	06	-
3e	04	09	12	16
Amphotericin B	08	04	10	12



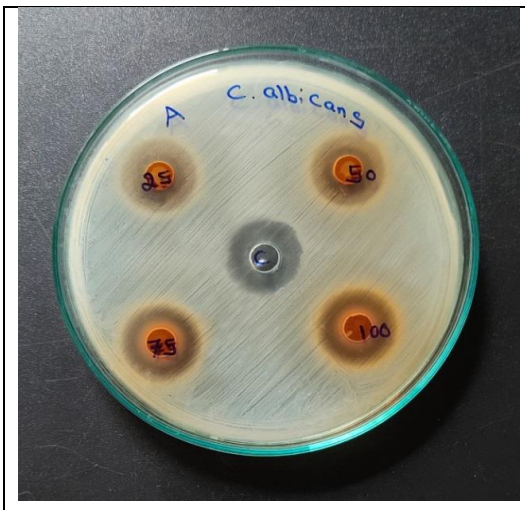
Complex (1c)



Complex (2a)

Complex (3b)

Fig. 71. Antifungal activity on *A. niger*



Complex (1a)

Complex (2b)

Complex (2e)

Fig. 72. Antifungal activity on *C.albicans*

SUMMARY AND CONCLUSION

CHAPTER – VI

SUMMARY AND CONCLUSIONS

Chapter 1: Highlighted the brief introduction of coordination chemistry, importance of metal ions in human biology, mannich reaction, chemistry of amides and antimicrobial activity of metal complexes. The aim and objective of the present work was described in **chapter 2**.

Chapter 3: This chapter focused on synthesis of mannich bases and its therapeutic importance, biological importance of mannich bases, applications of biologically active mannich base compounds, general review of urea and substituted urea connected metal complexes, general investigation of semi- and thiosemicarbazide derivatives of metal complexes.

Chapter 4: This chapter focused on the synthesis of mannich base ligands namely, 2-((2,6-dioxocyclohexyl)(2-hydroxyphenyl)methyl)hydrazine carboxamide (CMC), 1-((2,6-dioxocyclohexyl)(2-hydroxyphenyl)methyl)urea (CMU) and 1-((2,6-dioxocyclohexyl)(2-hydroxyphenyl)methyl)thiourea and its spectral data. Synthesis of metal complexes (**1a-e**), (**2a-e),** (**3a-e**) and its respective flowchart of the synthetic protocol was also described. The characterization techniques like, solubility measurements, melting point, magnetic susceptibility, Spectroscopic techniques and

detailed experimental procedure for antimicrobial activity were also explained in details.

Chapter 5: The findings of research on metal complexes of novel Mannich bases generated from semicarbazide, urea, and thiourea are presented in this chapter. Electrical conductance assessments of 10^{-3} M solutions of the complexes in DMSO show that all the complexes are non-electrolytes. The spectrum observations show that CMU acts primarily as a chelating bidentate ligand, coordinating one of the carbonyl O atoms and the O atom of the salicylaldehyde moiety in all of the metal complexes (**1a-1e**) examined. The alterations in the stretching frequencies of functional groups containing the donor atoms are used to infer coordination modes. The presence of M-O, M-N, and M-X bonds (X= halogen) in the complexes is shown by far IR spectral data. To determine the stereochemistry surrounding the metal ion in each compound, electronic spectrum measurements in solutions were performed. All of the synthesised complexes had 6-coordinated octahedral geometry, based on the number, energy locations, and intensities of the absorption bands. The complexes' magnetic susceptibility observations indicate that all of them are paramagnetic. The quantity of unpaired electrons determined from magnetic moment data adds to the validity of the suggested coordination geometry. EPR spectrum analyses and other spectral parameters have been estimated to get a better

understanding of the nature of bonding and geometry in CuII complexes. The covalent character of all the CuII complexes is shown by the $g_{\parallel}$, $g^{\perp}$ and G values.

The *in vitro* antimicrobial screening of all the ligands and its metal complexes. The antibacterial activity of the synthesized ligand (**1-3**) and complexes (**1a-1e**), (**2a-2e**), (**3a-3e**) were tested. The ligands (**1-3**) had low activity compared to the corresponding complexes (**1a-1e**). In comparison to complexes (**1a-1e**), complex **1a** (Cu II), complex **1c** (Fe II), and complex **1d** (Cr II), has exceptional activity. In the (**2a-2e**), series, the complex **2b** was only highly active, with an MIC of 2 µg/mL in *S. aureus*. Obviously, the copper complex **2a** was more active against *K. pneumoniae*, with MIC of 4 µg/mL, than the control **Ciprofloxacin**, which had MIC of 8 µg/mL. In comparison to complexes (**2a-2e**), complex **2a** (Cu II), complex **2b** (Ni II), and complex **2e** (Mn II), has exceptional activity. In the (**3a-3e**), series, the complex **3c** was only highly active, with an MIC of 2 µg/mL in *S. aureus*. In comparison to complexes (**3a-3e**), complex **3c** (Fe II), complex **3d** (Cr II), and complex **3e** (Mn II), has exceptional activity.

The antifungal activity of the synthesised ligands (**1-3**) and their complexes (**1a-1e**), (**2a-2e**), and (**3a-3e**) was investigated. In comparison to the comparable complexes, the ligands (**1-3**) displayed poor activity (**1a-1e**). The complex **1a** in the (**1a-1e**) sequence was only moderately active in *C. albicans*, with a MIC of 6 g/mL.

Complex **1a** (Cu II), complex **1b** (Ni II), and complex **1c** (Fe II) have extraordinary activity when compared to complexes (**1a-1e**). The complex **2b** was only moderately active in the (**2a-2e**) group, with a MIC of 6g/mL in *C. albicans*. Complex **2a** (Cu II), complex **2b** (Ni II), **2c** (Fe II), and complex **2d** (Cr II) have extraordinary activity when compared to complexes (**2a-2e**). The complex **3e** of the (**3a-3e**) group was only reasonably active in *C. albicans*, with a MIC of 4 g/mL. With a MIC of 3 g/mL, the iron complex **3c** was clearly more potent towards *C. neoformans* than the standard **Amphotericin B**, which had a MIC of 4 g/mL. Complex **3e** (Mn II), complex **3c** (Fe II), complex **3d** (Cr II), and complex **3b** (Ni II) have extraordinary activity when compared to complexes (**3a-3e**).

SCOPE FOR FUTURE WORK

1. The work can be extended to analyze the cytotoxic activity of other ligands and to screen the compounds for other biological activities such as anti-inflammatory, antihypertensive activities etc.

2. The metal complexes' selectivity for CT-DNA actions may be changed, laying the groundwork for the rational creation of new, powerful agents for exploring and directing nucleic acids.

3. To encourage more effective nuclease action, adjusting the reactivity of the metal centers in a range of ligand settings may make significant progress.

4. In the future, a far more thorough examination of the kinetic and mechanistic characteristics of these processes will be possible.

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CHAPTER - VII

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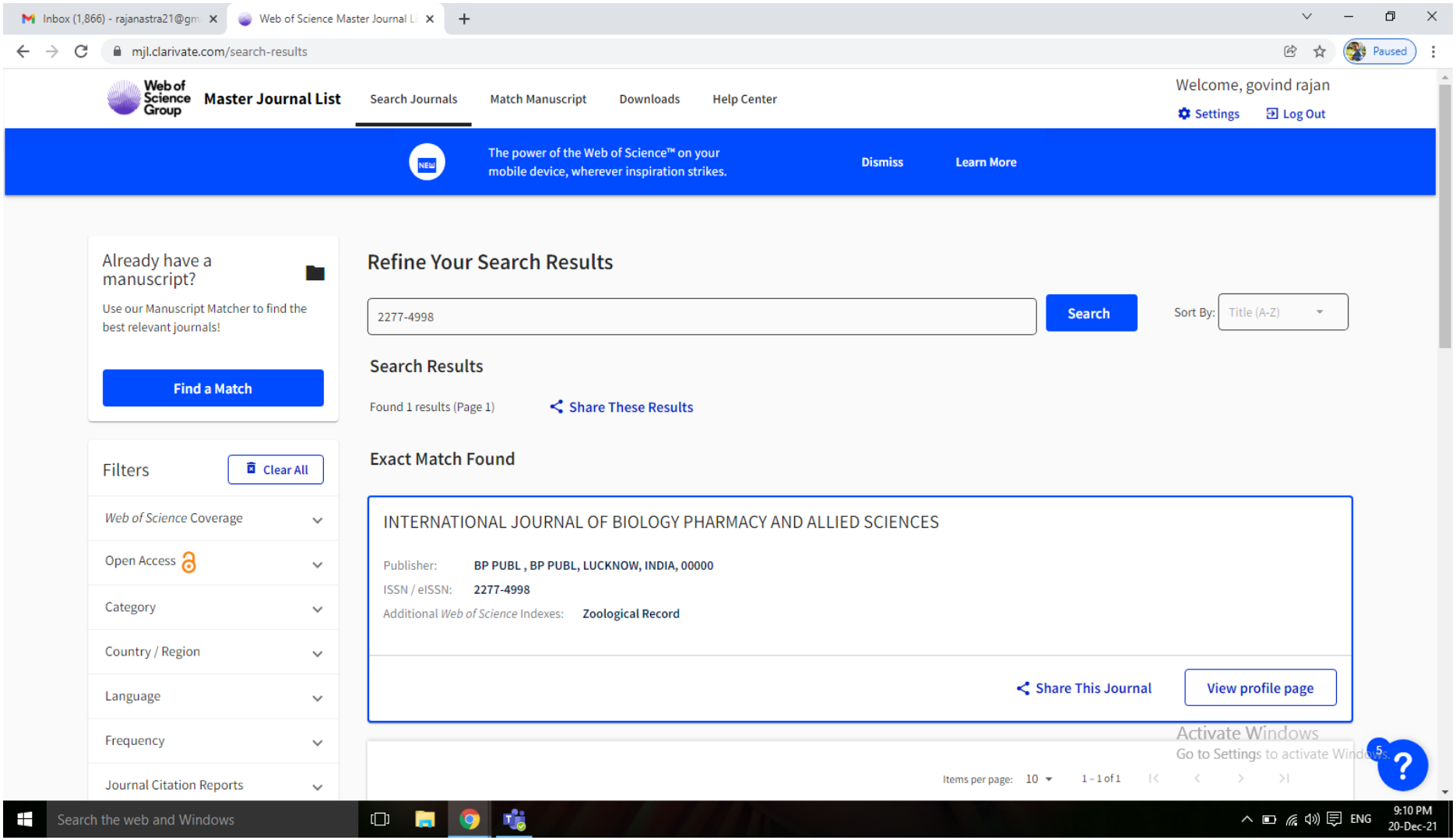
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DESIGN, SYNTHESIS, CHARACTERIZATION, AND BIOLOGICAL ACTIVITY OF SOME TRANSITION METAL COMPLEXES VIA NOVEL MANNICH BASE LIGAND

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ABSTRACT

From the mannich base 2-((2,6-dioxocyclohexyl) (2-hydroxyphenyl) methyl) hydrazine carboxamide (**1**), a series of metal(II) complexes (**1a-1e**) ML with M = Cu(II), Ni(II), Fe(II), Cr(II), and Mn(II) were prepared and studied by electronic, IR, and NMR (^{1}H & ^{13}C) spectra, and molar conductivity measurements. The complexes are nonelectrolytes, according to conductivity measurements. All complexes have octahedral geometry, according to spectroscopy and other analytical investigations. The disc diffusion technique was used to test the antibacterial activity of ligand (**1**) and metal complexes (**1a-1e**) against *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumaniae*, and *Pseudomonas aeruginosa*. The metal complexes (**1a-1e**) were more effective than the control **Ciprofloxacin**.

Keywords: Mannich base, Transition metal complexes, Antibacterial activity, *Staphylococcus aureus*

INTRODUCTION

An acidic proton adjacent to a carbonyl group is amino alkylated with formaldehyde and ammonia or any primary or secondary amine in the Mannich reaction. A β-amino carbonyl molecule is the end result. Mannich reactions have also been proposed for

reactions involving imides and aromatic aldehydes. A survey of the literature on Mannich reactions reveals a large volume on the chemical, pharmacological, and toxicological characteristics of Mannich bases **[1-6]**, which have many uses as polymers, lubricant dispersants, and medicinal substances. Compounds with an amide moiety as a functional group were discovered to have donor characteristics and to have a broad variety of biological functions **[7-13]**. Transition metals are necessary for the proper functioning of living beings and also have a lot of promise as medicines **[14]**.

Owing to the sensitivity and selectivity of the ligands against different metal ions, metal complexes of Mannich bases were widely investigated in recent years **[15-19]**. Mannich process, to our understanding, is a three-component condensation process involving an active hydrogen-containing molecule, formaldehyde, and a secondary amine **[20]**. Extraction of solid complexes of various aromatic aldehydes or ketones, semicarbazones using transition metals has been studied extensively **[21, 22]**. There has been no research on the condensation of 1,3-cyclohexanedione, salicylaldehyde, and semicarbazide, according to the literature. The ability of semicarbazide compounds that contain the amide moiety to produce metal complexes is extensively documented in the literature. As a result, it was believed that synthesizing some metal complexes of this kind of Mannich base and investigating its bonding properties would be interesting. The three-component condensation of active hydrogen on 1,3-cyclohexanedione, salicylaldehyde, and semicarbazide yields 2-((2,6-dioxocyclohexyl) (2-hydroxyphenyl) methyl) hydrazine carboxamide (**1**), which we describe here. Monocoordination occurs in this ligand system owing to the O atom of semicarbazide.

Experimental

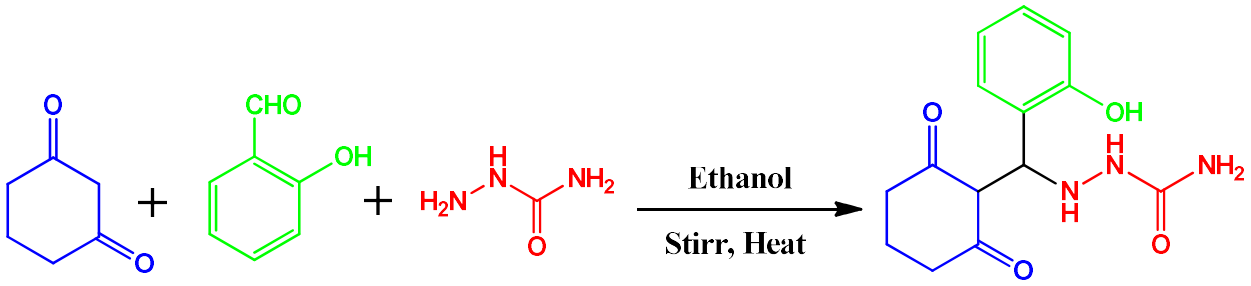
Chemicals and reagents

Merck and Sigma-Aldrich provided all of the chemicals, which were utilized without additional cleanup. The solvents have been purified and distilled before use. Merck's pre-coated silica gel plates with a fluorescent indication were utilized for analytical TLC. Silica gel chromatography of the flash column (Merck). The eluting solvent for TLC and column chromatography was ethyl acetate-hexane. Melting points were recorded in open capillary tubes and were not adjusted. The UV-Visible spectrum was obtained using a Shimadzu UV - 1280 (200-800 nm) spectrophotometer. The FT-IR

spectra (KBr) are obtained using a Shimadzu 8201pc (4000-400 cm-1) spectrophotometer.

Synthesis of Ligand (1)

In a 100mL RB flask, 1,3-cyclohexanedione (5.60 g, 0.05 mol), salicylaldehyde (6.1 mL, 0.05 mol), and Semicarbazide (0.05 mol, 5.57 g) were dissolved in 20mL ethanol. The contents of the flask are thoroughly stirred after 30 minutes of heating using a magnetic stirrer. After then, a brilliant crimson residue appeared. It has been dried and filtered. To produce pure product, the final prepared sample was recrystallized in hot ethanol. In **Scheme 1**, the production of ligand 1 is shown.



Scheme. 1. Synthesis of ligand 1

4.2.1.1. 2-((2,6-dioxocyclohexyl)(2-hydroxyphenyl) methyl) hydrazine carboxamide (1)

Red solid; mw: 291.30; mp:184°C; IR (KBr cm^{-1}) ν_{max}: 3435.94 (-OH), 2950.12 (-NH), 1638.73 (-C=O), 1237.44 (-C-N-C); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.08 (s, 1H, NH), 7.12-6.90 (m, 4H, Ph-OH), 6.81 (d, *J* = 1.4 Hz ,1H, NH), 6.25 (s, 2H,NH_2), 5.64 (s, 1H, OH), 5.32 (d, *J* = 1.7 Hz, 1H, CH-Ph), 4.34 (d, *J* = 6.9 Hz, 1H, CHD), 2.47-1.95 (m, 6H, CHD); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 208.83 (2C, C=O), 157.43 (1C, C=O), 154.01 (1C, C-OH), 130.19, 128.12, 126.56, 121.18, 115.72 (5C, Ar ring), 69.81 (1C, CH), 45.61 (1C, CH), 40.85 (2C, CH_2), 16.57 (1C, CH_2); EI-MS: m/z 292.13 (M^+,15%); Elemental analysis: Anal. Calcd. for $C_{14}H_{17}N_3O_4$: C, 57.72; H, 5.88; N, 14.42;%. Found: C, 57.70; H, 5.84; N, 14.48;%.

Synthesis of metal complexes (1a-1e)

Under continuous stirring, ligand **1** of hot ethanolic solution of (2 equivalent, 0.02 mol) was progressively combined with a metal chlorides in hot ethanolic solution (1 equivalent, 0.01 mol) under reflux. After refluxing for 1-2 hours, the mixture was chilled and stored in the refrigerator for a few hours. In each instance, the colored solid complexes were separated. It was filtered before being rinsed with 50% alcohol and dried.

Antibacterial activity

Antibacterial assessments of the ligand (**1**) and its complexes (**1a-1e**) were experienced in vitro against the bacteria *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumaniae*, and *Pseudomonas aeruginosa* by Kirby Bauer Disc diffusion method [23]. The antibacterial activity of ciprofloxacin was utilized as a reference. The bacterial cultures were cultivated on petri dishes on nutrient agar medium. The compounds were synthesized in DMSO and immersed in a 5 mm diameter, 1 mm thick filter paper disc. After 24 hours, the width of the inhibitory zone [24,25] surrounding each disc was evaluated for antibacterial activity, and the discs were put on the already implanted plates and incubated at 37°C. Minimum inhibitory concentrations (MIC) were used to reflect the antibacterial activity of ligand (**1**) and its metal complexes (**1a-1e**).

Results and discussion

Metal complexes (1a-1e) with ligand (1)

Physical data

Table 1 shows the physical belongings of the complexes (**1a-1e**) generated from ligand (**1**).

Solubility

The solubility of the ligand (**1**) and its associated complexes (**1a-1e**) in various solvents was investigated, and the findings are shown in **Table 2**. The ligand (**1**) as well as the metal complexes (**1a-1e**) soluble more readily in aprotic solvents than in protic solvents, according to solubility experiments.

Conductivity measurements

Numerous solvents, including water, ethanol, chloroform, and DMSO, were used to test the solubility of the newly synthesized metal complexes. The Equiptronics digital conductivity meter (Model EQ-660) was used to determine molar conductance in DMSO, with the cell constant calibrated using 0.1M KCl solution. The electrical conductivity of a 10^{-3} M solution of respective complexes in DMSO were determined, revealing the complexes' neutral (non-electrolytic) character. The molar conductance of the mixed ligand complexes (**1a-1e**) of ligand (**1**) ranges from 18 to 28 $\Omega^{-1}mol^{-1}cm^2$. The chloride ions were shown to be coupled to metal ions via conductivity tests, suggesting that they function as ligands rather than ions. Components for the produced complexes were selected depending on the metal – ligand ratios (1:2) and the type of the electrolytes as determined by conductance experiments, which aids in determining the structure of the complexes. The conductance properties of metal complexes (**1a-1e**) with ligand (**1**) were shown in **Table 3**.

NMR Spectral studies of ligand (1)

The hydrogens of the aromatic rings show a multiplet at 7.12-6.90 ppm in the ^{1}H NMR spectrum of the Mannich base ligand (**1**) below investigation **(Figure 1)**. The methylene hydrogens linked to the salicylaldehyde and amine hydrogens of the semicarbazide show as a peak at 4.34 ppm, whereas the aromatic –OH occurs at 5.64 ppm. The absence of an indication equivalent to the secondary amine $–NH_2$ proton as it was removed in the Mannich process further confirms the creation of the ligand. The carbons of the aromatic rings had peaks at 130.19-115.72 ppm in the ^{13}C NMR spectra of the Mannich base ligand (**1**) under investigation **(Figure 2)**. The presence of a peak at 45.61 ppm shows that the methylene carbon is linked to the semicarbazide's salicylaldehyde and amine hydrogens, respectively. Furthermore, the carbonyl carbons of the 1,3-cyclohexanedione and semicarbazide moiety are represented by the peaks at 208.83 and 157.43 ppm, accordingly.

IR Spectra

The existence of a strong band at 3435.94 and 1638.73cm^{-1}, which is attributed to vOH and the C=O carbonyl group, is a significant finding in the ligand spectrum (Fig. 3). The bands attributable to C=O and O-H moved towards lower frequency in all of the complexes (Fig. 4-8), suggesting that carbonyl oxygen and hydroxyl oxygen were engaged in coordination through metal ions. In copper complex (**1a**), the M-O bond is represented by the new peak appeared at 757.42 cm^{-1}. The M-Cl bond is represented by the new peak at 526.68 cm^{-1}. The IR Spectral data of the complexes (**1a-1e**) and the ligand (**1**) were displayed in **Table 4**.

UV-Visible Spectra

The ligand and complex UV-visible spectra were obtained in the region of 100-1100 nm. The UV spectra of ligand (1) primarily revealed two strong maximum bands at 380nm and 525nm, which correspond to the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions, respectfully **(Figure 9)**. The octahedral geometry of the Cu (II) complex being investigation is suggested by a wide band in the 300nm range. The octahedral structure of the Ni (II) complex was confirmed by wide peaks at 263nm and 311nm. The octahedral structure of the bands found for Cr (II) complex also displays wide peaks at 263nm and 301nm. Broad signals were seen at 263nm and 321nm for the Fe (II) complex, confirming its octahedral shape. The Mn (II) complex emitted wide signals at 262 nm, indicating that it is octahedral. **Figure 10-14** shows the UV spectrums of metal complexes (**1a-1e**).

EPR spectra

The type of metal ligand bond formation along with the dispersion of paired and unpaired electrons may be learned through EPR spectrum analysis. Cu (II) complexes have a unique character in coordination chemistry, with geometries such as tetrahedral, square planar, octahedral, and square pyramidal that may be distinguished by EPR spectrometry. $g\parallel$, $g\perp$, gavg and G are EPR parameters that indicate if the compound is octahedral or tetrahedral. The following criterion confirms the existence of an unpaired electron in the dx^2-y^2 orbital: $g\parallel > g\perp > 2.0023$. For the copper complex, the measured $g\parallel$ and $g\perp$ values are 2.1581 and 2.0138, correspondingly. The ionic nature is shown by a $g\parallel$ value more than 2.3, while the covalent nature is indicated by a $g\parallel$ value less than 2.3. We can see that the $g\parallel$ value (2.1581) is smaller than 2.3, indicating that the compound is covalent. According to Hathaway, G values less than four indicate a significant exchange contact between metal centers, whereas G values higher than four indicate a minimal charge transfer. The G value is 4.76 in this case, thus the exchange interaction is insignificant. The Cu (II) complex exhibits deformed octahedral geometry, according to the EPR characteristics. The EPR spectra of copper complex (**1a**) was shown in **Figure 15**.

Suggested Structure of the Complexes

We propose the following structure of complexes produced with the Mannich base ligand based on the preceding findings.

Biological screening

Antibacterial activity

The antibacterial activity of the synthesized ligand (**1**) and complexes (**1a-1e**) were tested. The ligand (**1**) had low activity compared to the corresponding complexes (**1a-1e**). The investigation was done in a controlled environment. In the (**1a-1e**), series, the complex **1a** was only highly active, with an MIC value of 2 µg/mL in *S.aureus*. Obviously, the chromium complex **1d** was more active against *K.neumoniae*, with MIC value of 4 µg/mL, than the control **Ciprofloxacin**, which had MIC value of 8 µg/mL. The iron complex **1c** was more active against *E.coli*, with MIC value of 4 µg/mL, than the control **Ciprofloxacin**, which had MIC value of 6 µg/mL. In comparison to complexes (**1a-1e**), complex **1a** (Cu II), complex **1c** (Fe II), and complex **1d** (Cr II), has exceptional activity. **Table 5** summarizes the findings.

Table 1: Physical data of the complexes (1a-1e) and ligand (1)

Compound	Colour	Melting point (^{o}C)
Ligand (1)	Red	184
Copper complex (1a)	Blue	210
Nickel complex (1b)	Pale green	214
Iron complex (1c)	Brown	226
Chromium complex (1d)	Green	208
Manganese complex (1e)	White	220

Table 2: Solubility test results

Compound	Water	Ethanol	Chloroform	DMSO
Ligand (1)	Insoluble	Insoluble	Sparingly soluble	Soluble
Copper complex (1a)	Insoluble	Insoluble	Insoluble	Soluble
Nickel complex (1b)	Insoluble	Insoluble	Insoluble	Soluble
Iron complex (1c)	Insoluble	Insoluble	Insoluble	Soluble
Chromium complex (1d)	Insoluble	Insoluble	Insoluble	Soluble
Manganese complex (1e)	Insoluble	Insoluble	Insoluble	Soluble

Table 3: Conductance properties of metal complexes (1a-1e) with ligand (1)

S. No	Compounds	Conductance ($\Omega^{-1}mol^{-1}cm^{2}$)
1.	Copper complex (1a)	18
2.	Nickel complex (1b)	28
3.	Iron complex (1c)	24
4.	Chromium complex (1d)	22
5.	Manganese complex (1e)	23

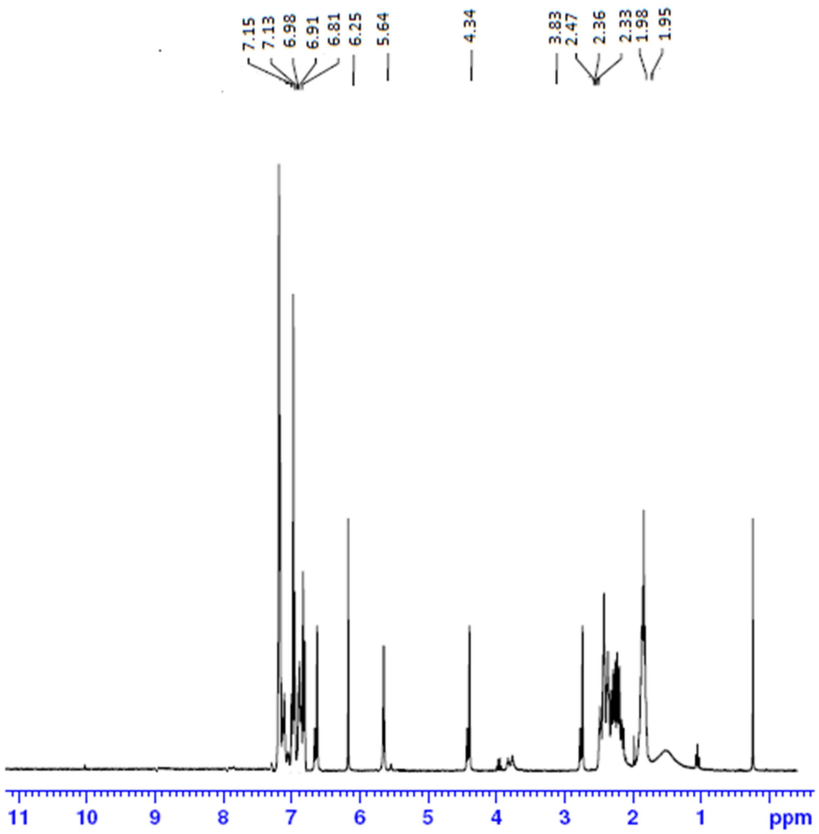


Figure 1: Ligand (1)-^{1}H-NMR spectra

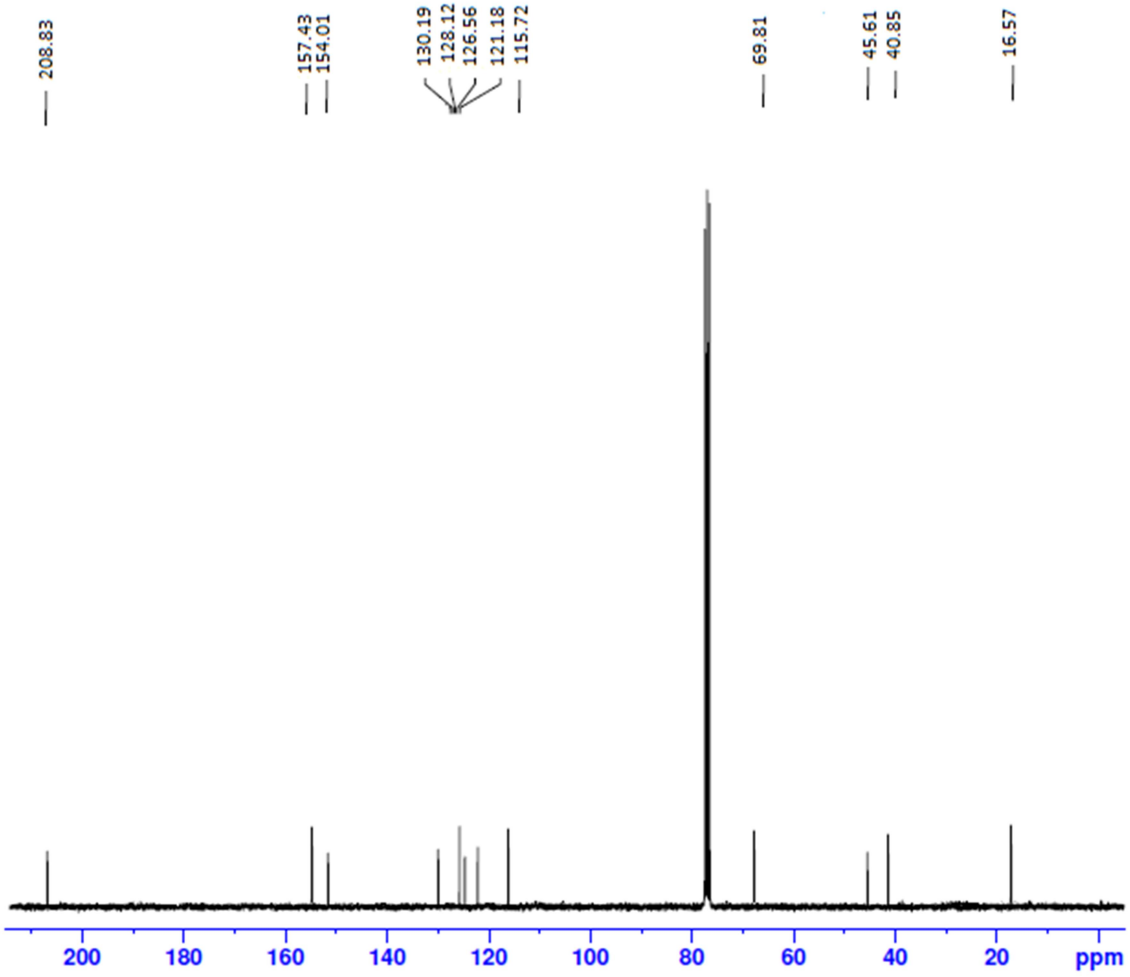


Figure 2: Ligand (1)-^{13}C-NMR spectra

Table 4: IR Spectral data of the complexes (1a-1e) and the ligand (1)

	IR stretching frequency (cm^{-1})			
Compound	**-OH**	**-C=O**	**M-O**	**M-Cl**
Ligand (1)	**3435.94**	**1638.73**	**-**	**-**
Copper complex (1a)	**3392.75**	**1633.69**	**757.42**	**526.68**
Nickel complex (1b)	**3465.32**	**1624.01**	**755.22**	**546.16**
Iron complex (1c)	**3416.11**	**1640.87**	**758.19**	**525.93**
Chromium complex (1d)	**3431.63**	**1633.14**	**757.24**	**525.14**
Manganese complex (1e)	**3437.60**	**1642.27**	**757.74**	**525.25**

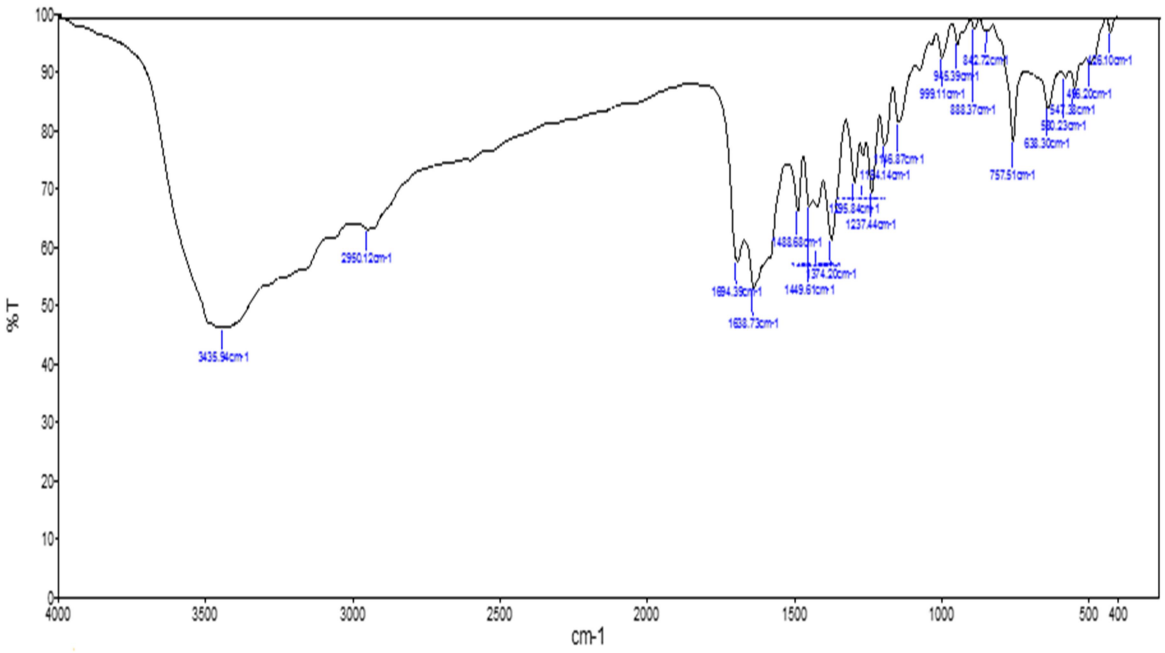


Figure 3: Ligand (1) FT-IR spectra

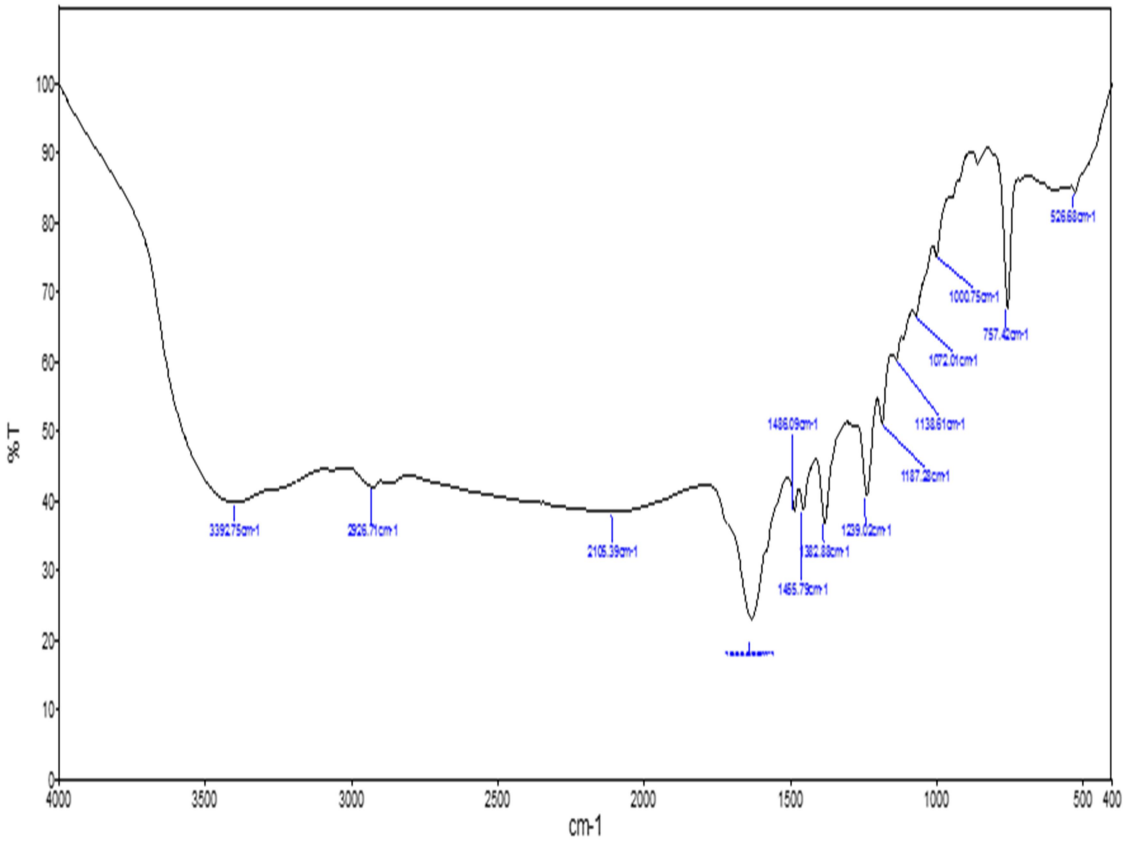


Figure 4: Copper complex (1a) FT-IR spectra

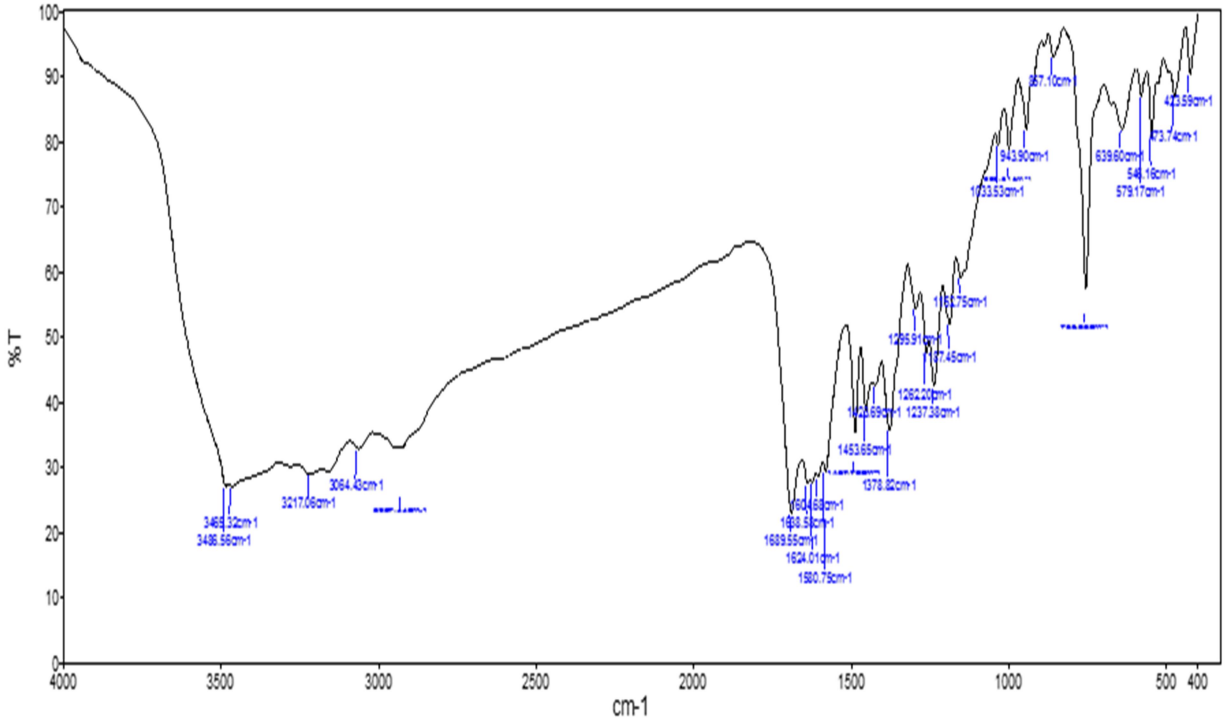


Figure 5: Nickel complex (1b) FT-IR spectra

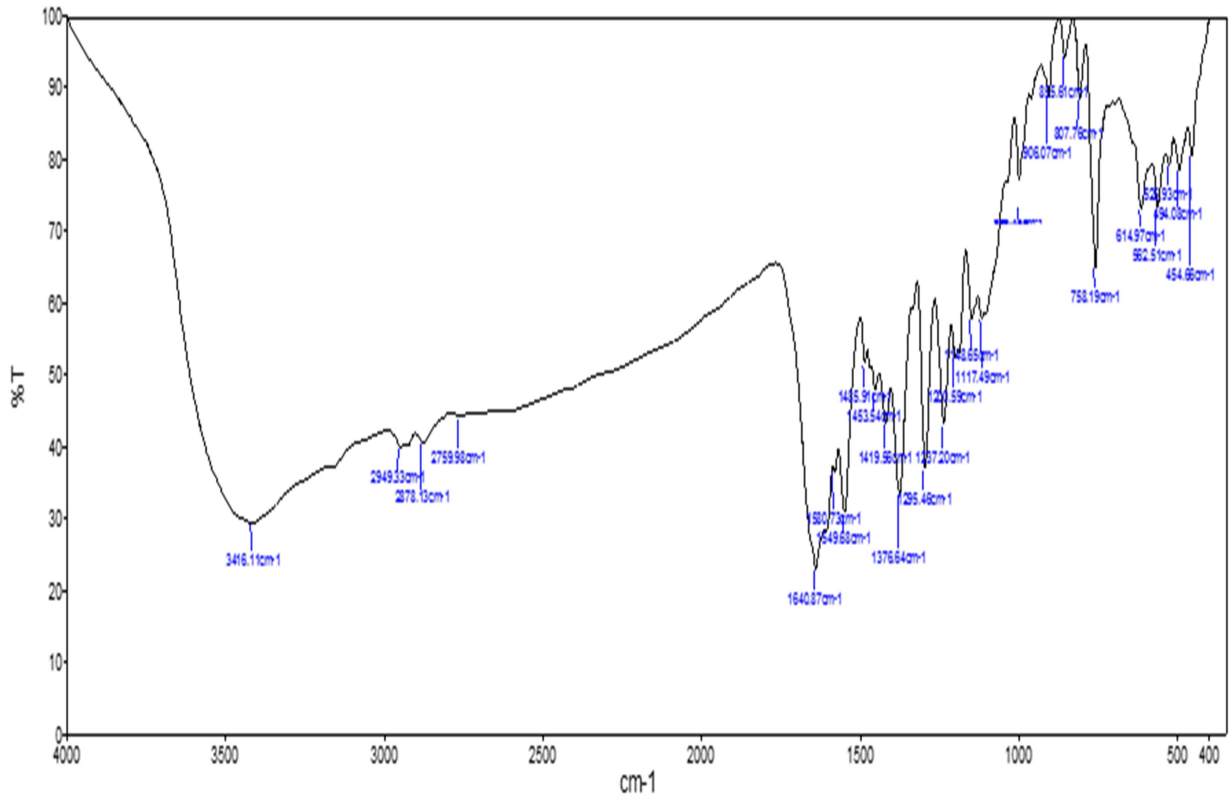


Figure 6: Iron complex (1c) FT-IR spectra

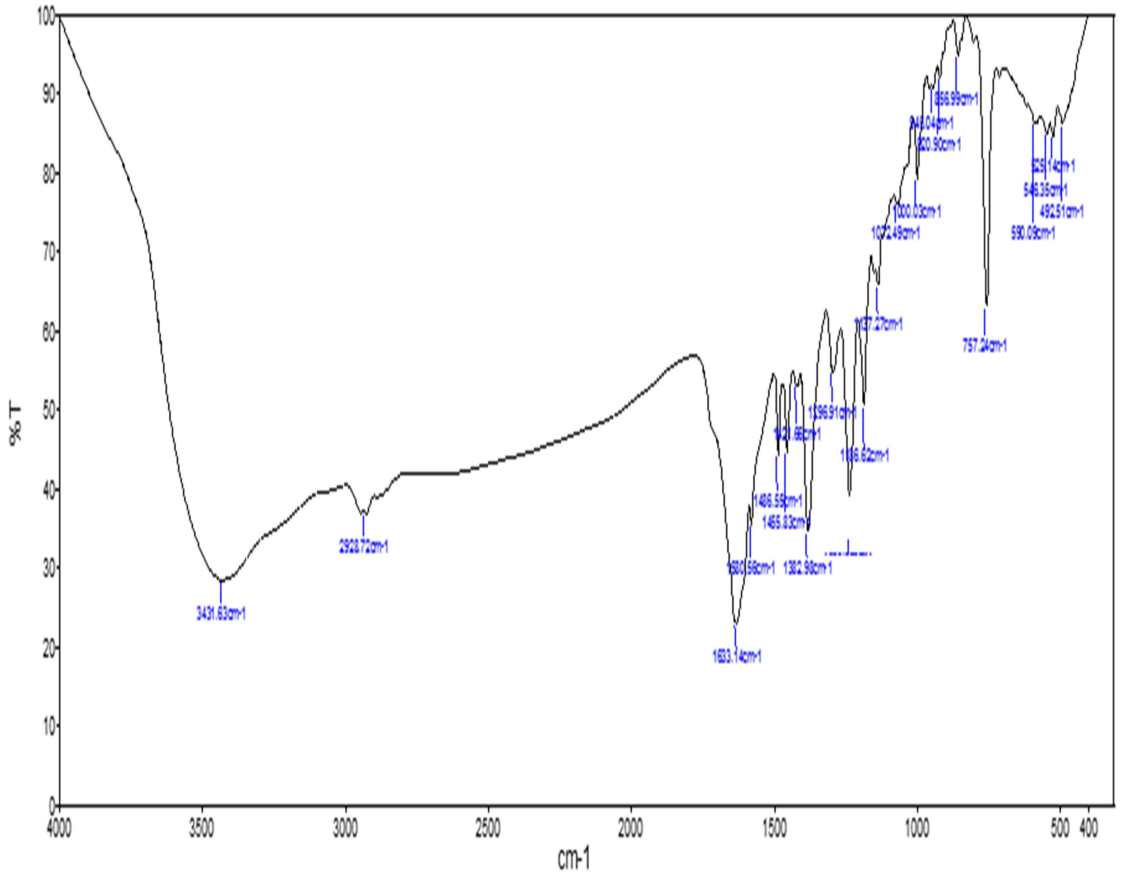


Figure 7: Chromium complex (1d) FT-IR spectra

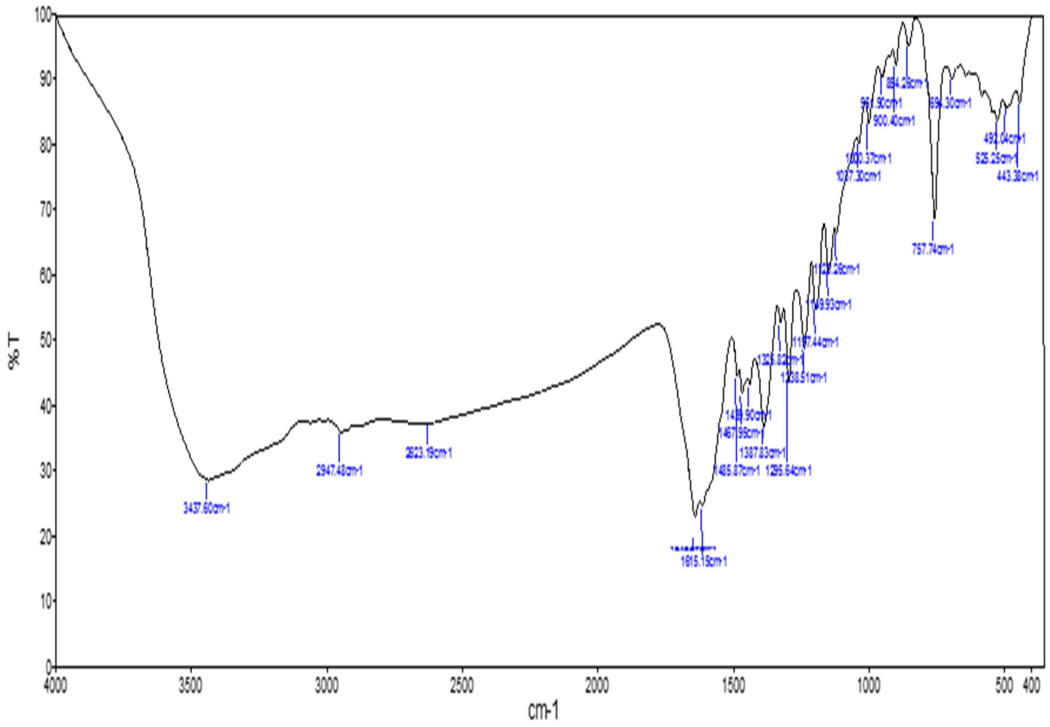


Figure 8: Manganese complex (1e) FT-IR spectra

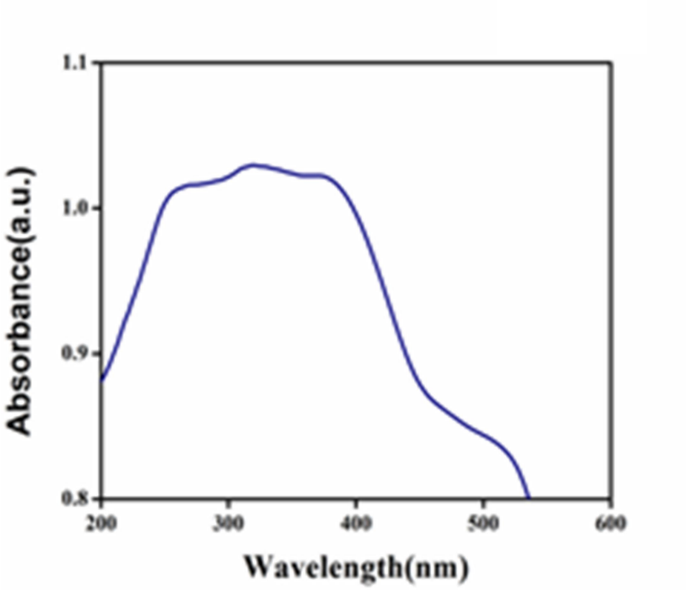


Figure 9: Ligand 1 UV-spectra

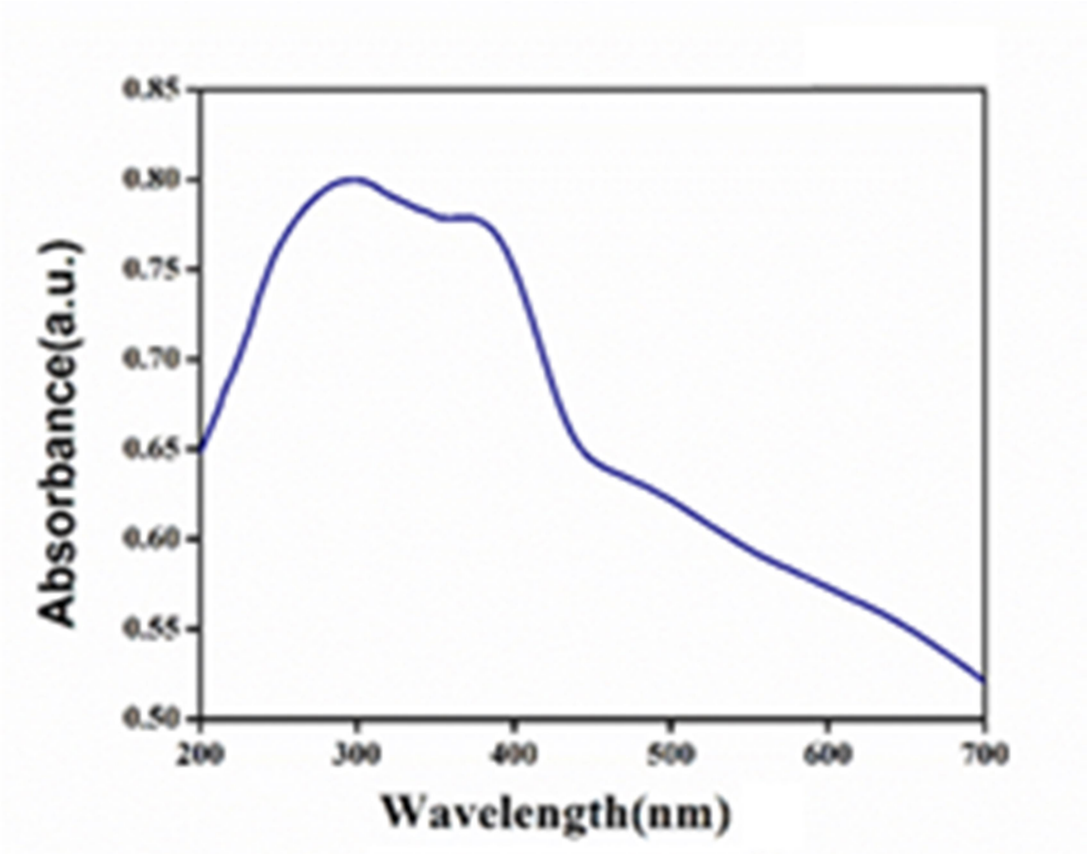


Figure 10: Copper complex (1a) UV-Spectra

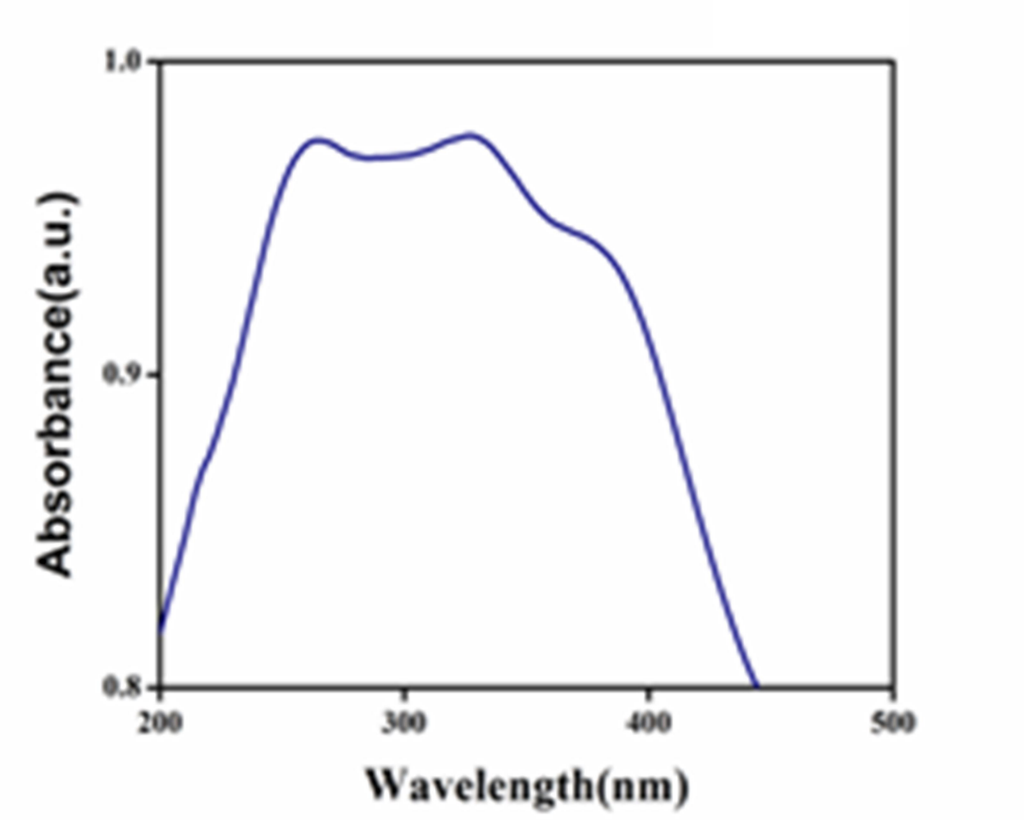


Figure 11: Nickel complex (1b) UV-Spectra

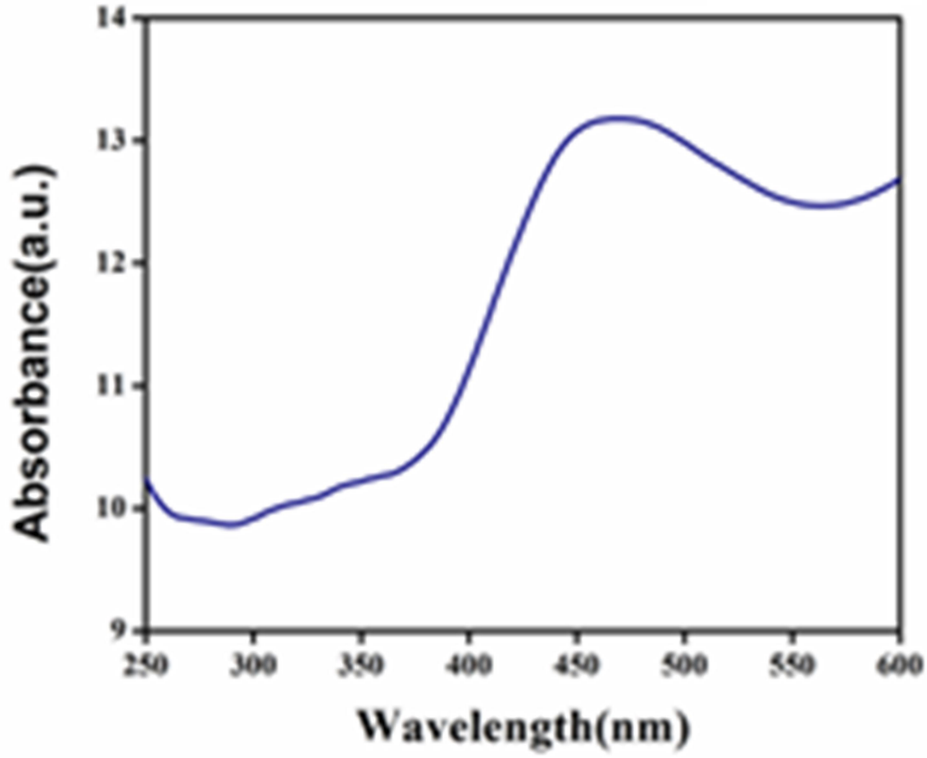


Figure 12: Iron complex (1c) UV-Spectra

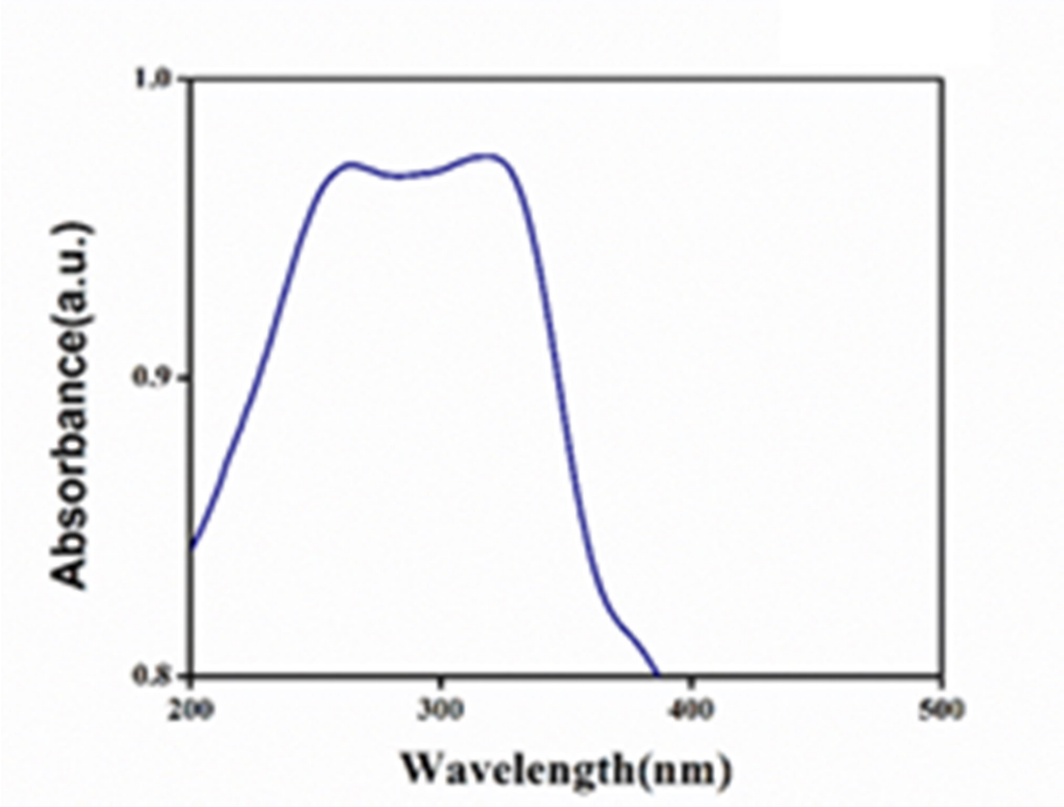


Figure 13: Chromium complex (1d) UV-Spectra

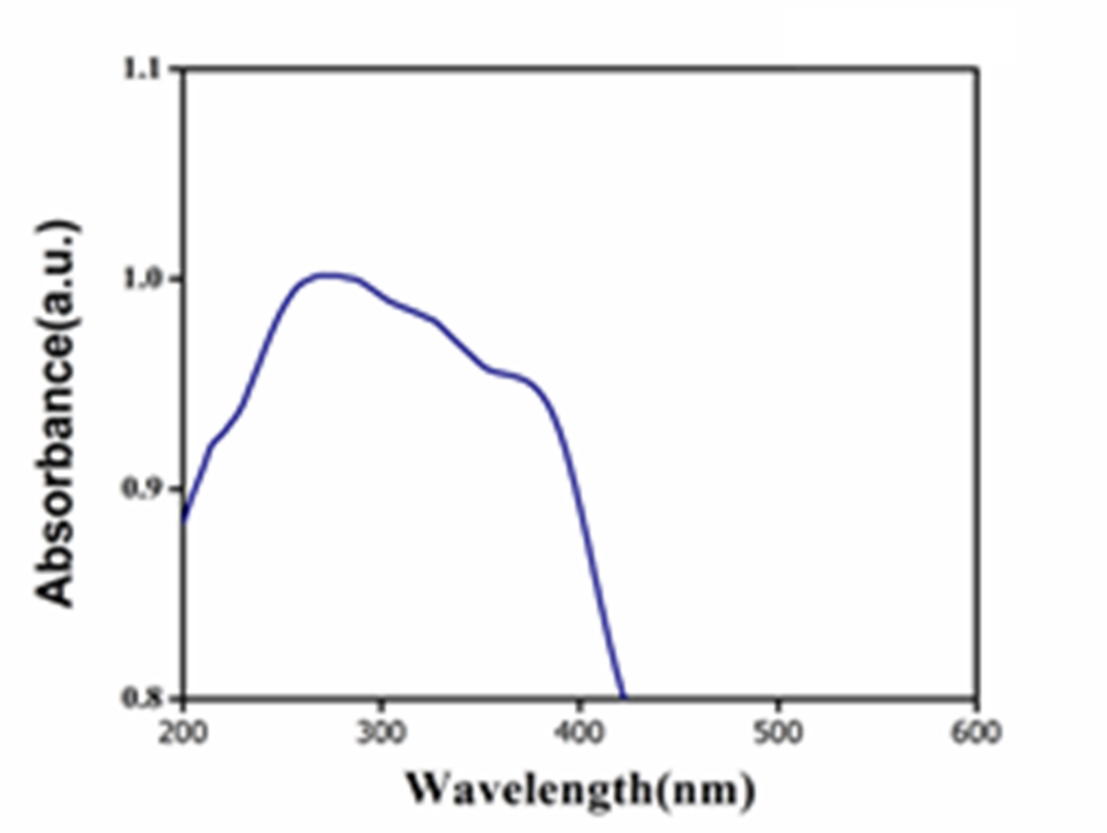


Figure 14: Manganese complex (1e) UV-Spectra

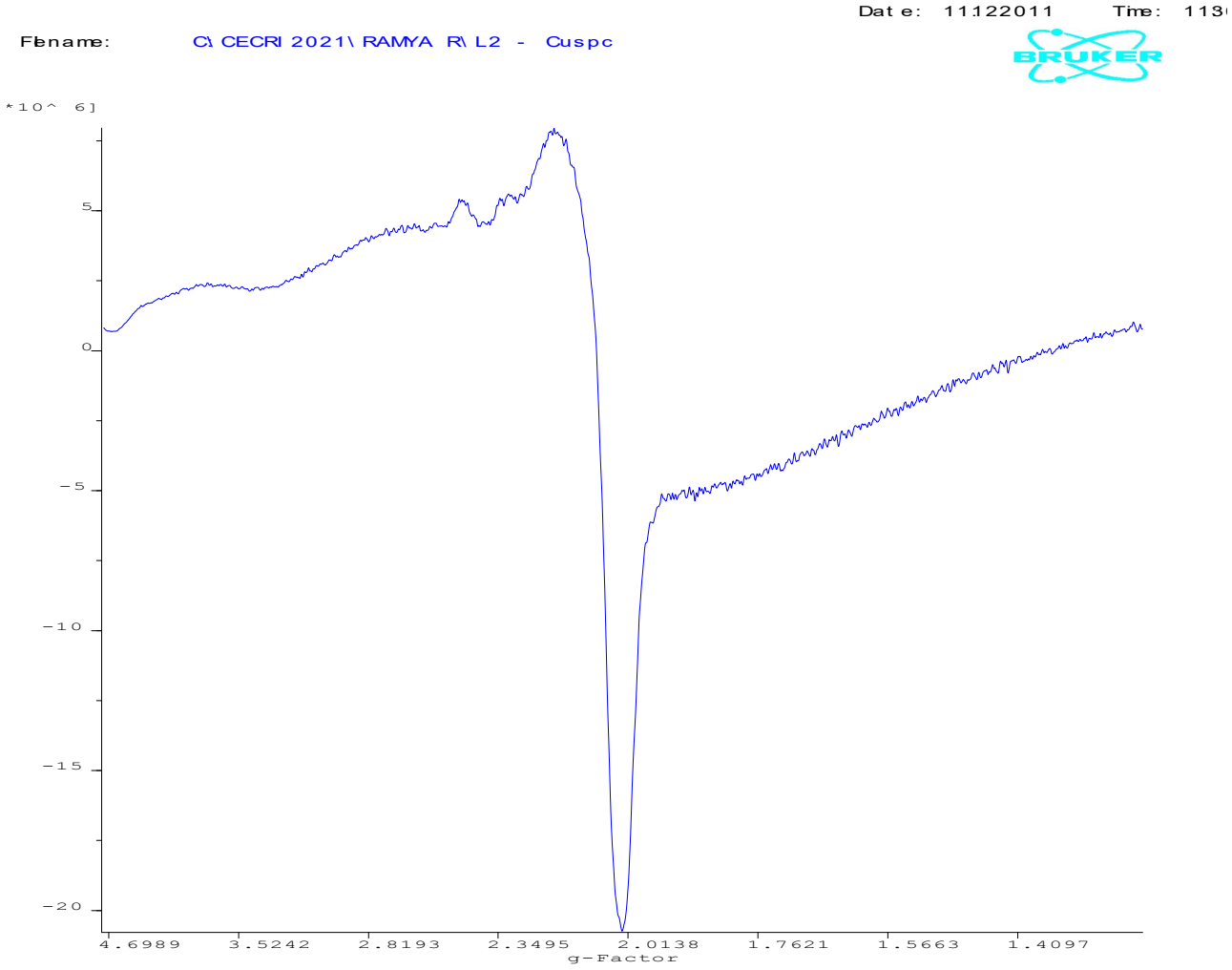
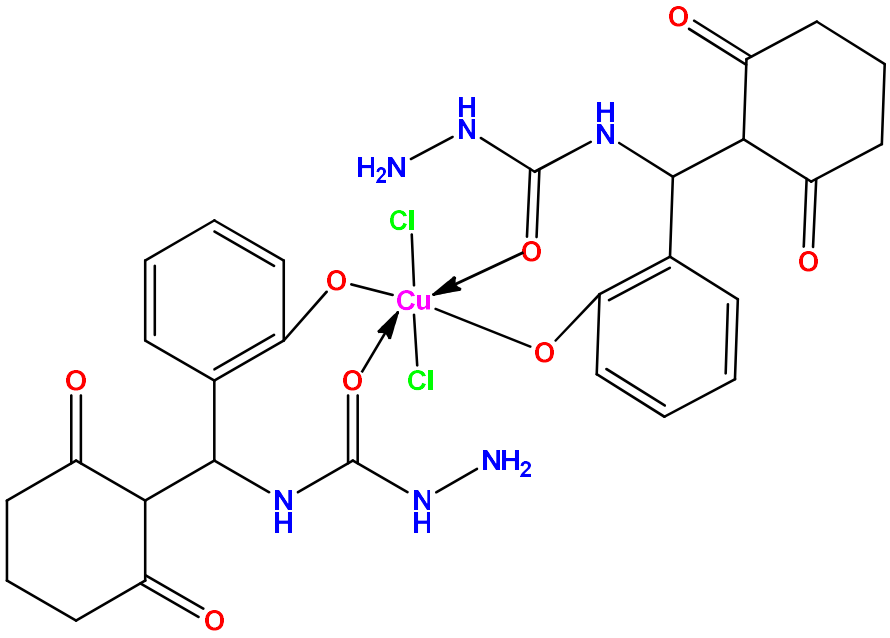
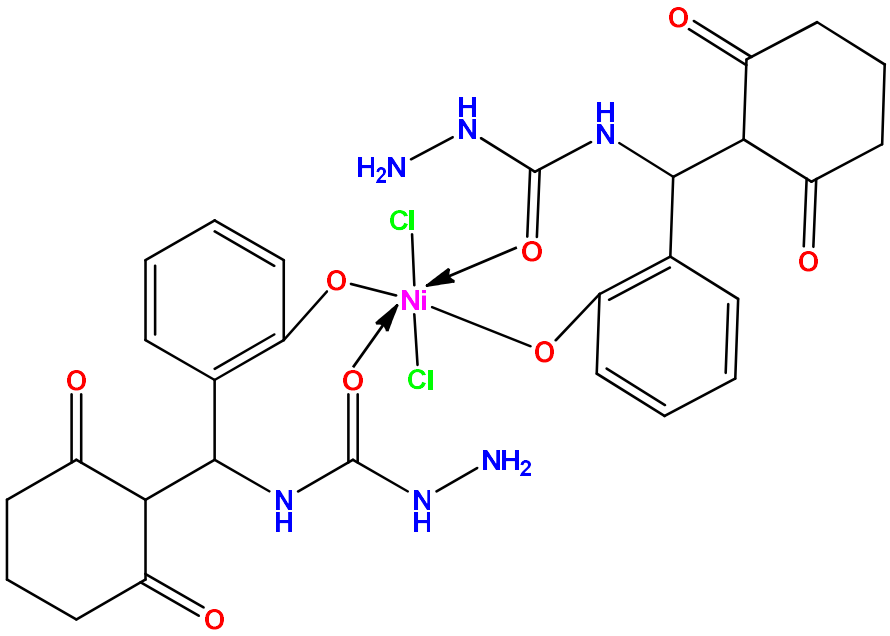


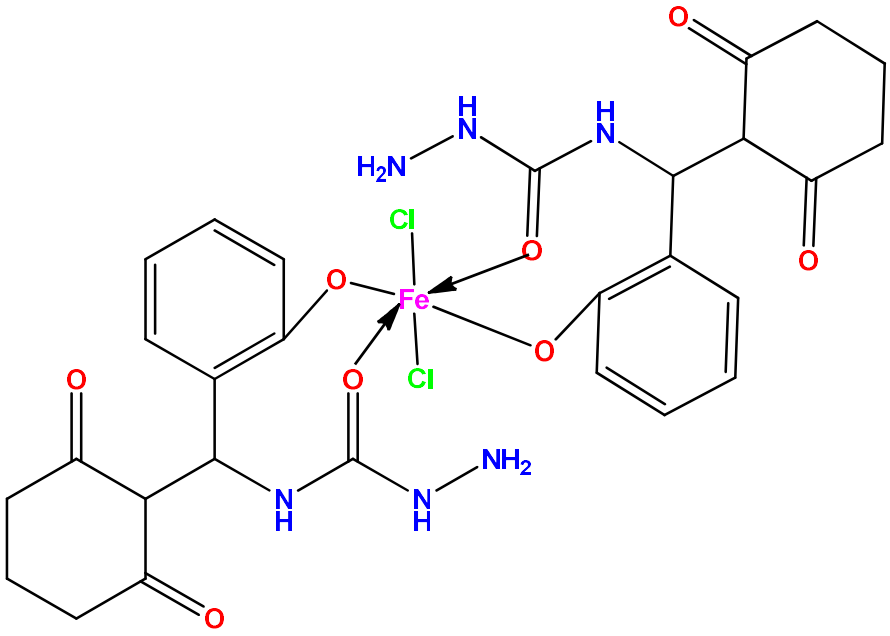
Figure 15: Copper complex (1a) EPR spectra



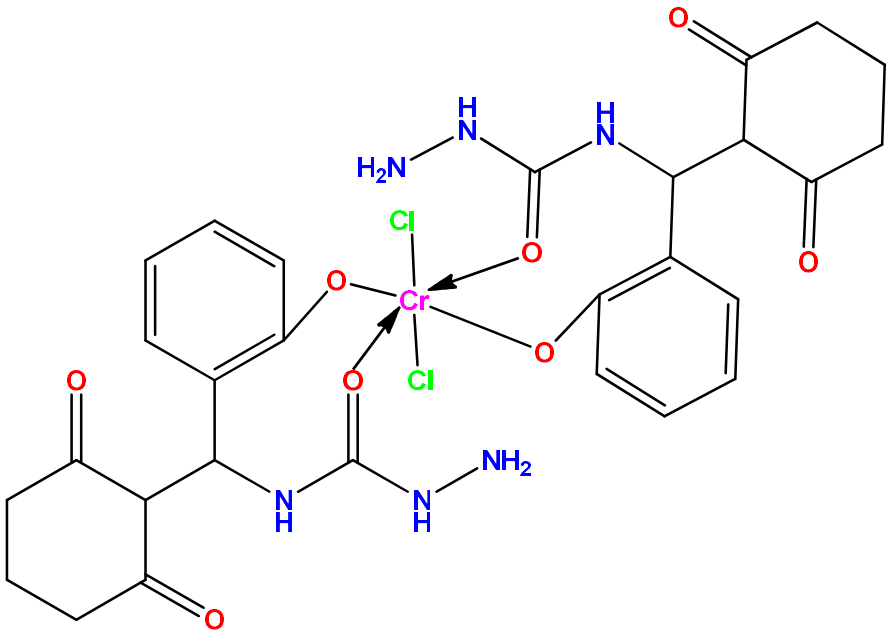
Structure of the Copper complex (1a) with ligand 1



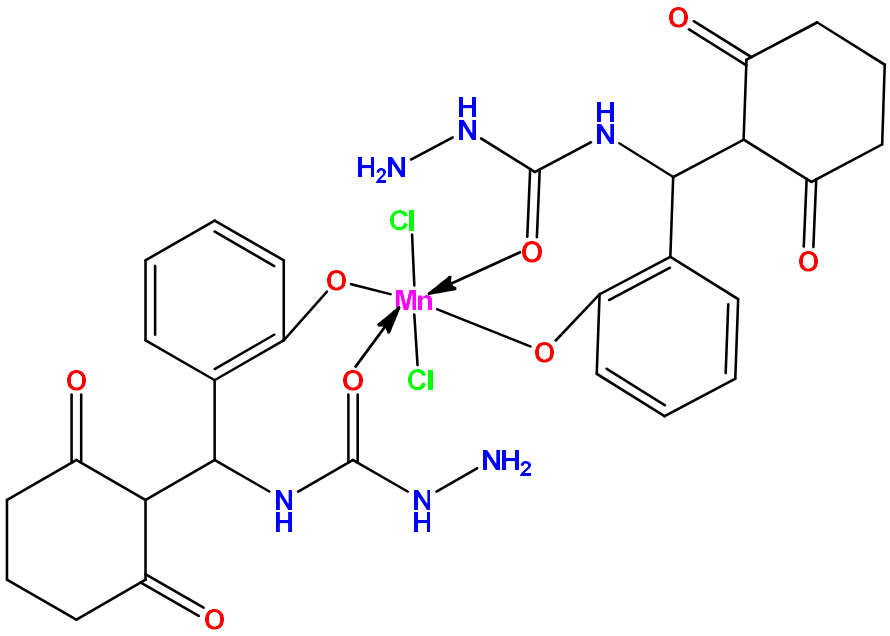
Structure of the Nickel complex (1b) with ligand 1



Structure of the Iron complex (1c) with ligand 1



Structure of the Chromium complex (1d) with ligand 1



Structure of the Manganese complex (1e) with ligand 1

Table 5: Antibacterial assessment of ligand (1) and its complexes (1a-1e)

Compounds	Minimum inhibitory concentration (MIC) in µg/mL			
	S. aureus	*K. pneumaniae*	*E. coli*	*P. aeruginosa*
1	32	16	16	32
1a	2	12	10	8
1b	8	28	8	8
1c	10	14	4	4
1d	6	4	12	4
1e	12	16	8	4
Ciprofloxacin	4	8	6	2

CONCLUSION

The coordination behavior of a Mannich base ligand synthesized from 1,3-cyclohexanedione, salicylaldehyde, and semicarbazide is reported in this article. Using the aforementioned Mannich base ligand, Cu (II), Ni (II), Fe (II), Cr (II), and Mn (II) complexes were produced and described using analytical and spectroscopic techniques. The Mannich base functions as a neutral bidentate ligand by coordinating to the metal ion via its semicarbazide oxygen and salicylaldehyde oxygen. The complexes are all octahedral in shape. The ligand (**1**) as well as its metal complexes (**1a-1e**) have been found to have considerable antibacterial action against several disease causing bacterial strains. Over **ciprofloxacin**, the metal complexes proved to be an effective bactericide.

Acknowledgments

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Conflicts of interest

The authors declare no conflicts of interest.

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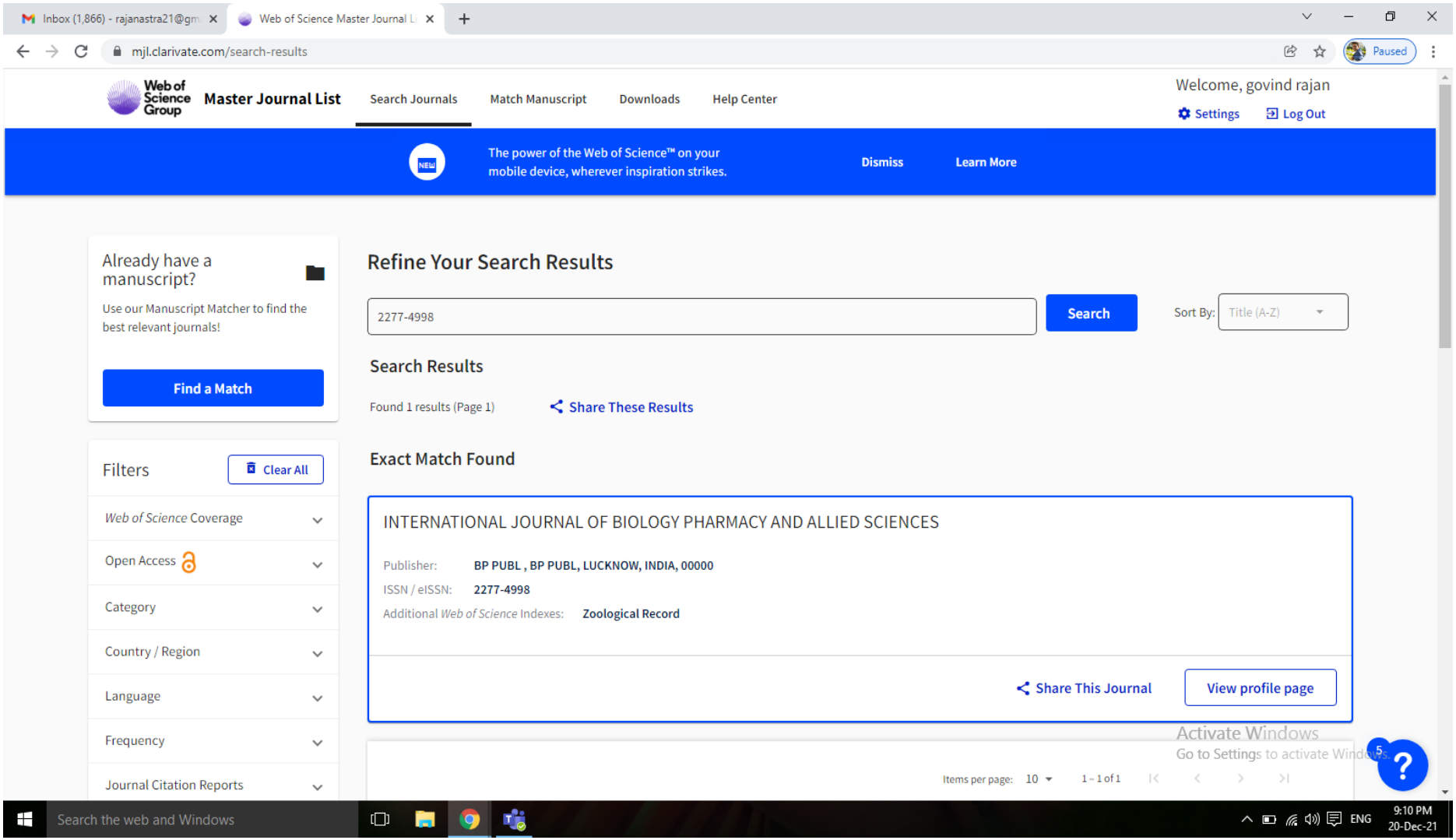
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SYNTHESIS, STRUCTURAL AND ANTIBACTERIAL STUDIES OF NOVEL MANNICH BASE LIGAND AND THEIR METAL COMPLEXES

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ABSTRACT

The condensation reaction of 1,3-cyclohexanedione, salicylaldehyde, and urea in the presence of ethanol as a solvent system yielded a novel mannich base, 1-((2,6-dioxocyclohexyl)(2-hydroxyphenyl)methyl)urea (**1**). UV-visible, FT-IR, ^{1}H & ^{13}C NMR, and elemental studies were used to determine the structure of ligand (**1**). IR and UV-visible spectra, molar conductivity, and EPR measurement were used to describe the structures of metal complexes (**1a-1e**) of the ligand (**1**). The geometries of all the complexes were octahedral. The antibacterial effect of ligand (**1**) and metal complexes (**1a-1e**) against *Pseudomonas aeruginosa, Escherichia coli*, *Staphylococcus aureus* and *Klebsiella pneumaniae* was investigated using the disc diffusion method. The metal complexes (**1a-1e**) were more significant than **Ciprofloxacin**, which served as a control.

Keywords: Antibacterial activity, Mannich base, *Staphylococcus aureus,* Transition metal complexes

INTRODUCTION

An acidic proton put adjacent to a carbonyl assembly is amino alkylated through ammonia and formaldehyde or some primary or secondary amine in the Mannich reaction.

A β-amino carbonyl molecule is the end result. Mannich processes were also proposed for reactions involving aromatic aldehydes and imides. A survey of the literature on Mannich reactions reveals a large amount of information on the biochemical, pharmacological, and toxicological properties of Mannich bases **[1-3]**.

Transition metals are necessary for the proper operational of alive things and consequently have a lot of promise as medicines **[4-7]**. The coordination behavior of nitrogen contributor Ligands is a fascinating subject to study. The complexes produced by 3d metals through bidentate Ligands utilizing together the nitrogen atoms of the ligands have received a lot of interest in this field. Metal chelates, instead of organic molecules, enhanced the action of many medicines **[8-13]**. To our knowledge, no research on this kind of metal complexes using the Mannich base Ligand has been undertaken.

In this paper, we describe the production of a novel Mannich base obtained from 1,3-cyclohexanedione, salicylaldehyde, urea, and metal complexes with Cu(II), Ni(II), Fe(II), Cr(II), and Mn(II) as part of our ongoing study. All of the metal complexes were described via the proper skills. Antibacterial activity was tested on all of the metal complexes.

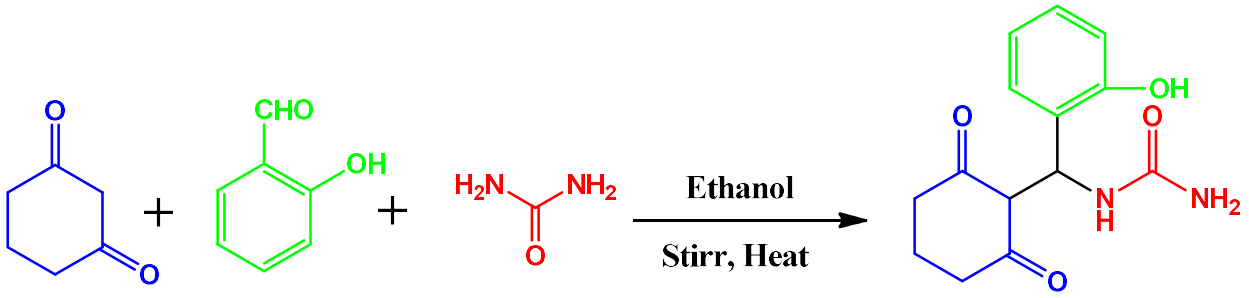
MATERIALS AND METHODS

Chemicals and reagents

Merck and Sigma-Aldrich provided all of the chemicals, which were utilized without additional cleanup. The solvents have been purified and distilled before use. Melting points were documented in open capillary tubes and were not adjusted. The UV-Visible spectrum was obtained using a Shimadzu UV - 1280 (200-800 nm) spectrophotometer. The FT-IR spectrum (KBr) are obtained using a Shimadzu 8201pc (4000-400 cm-1) spectrophotometer.

Synthesis of Ligand (1)

In a 100mL RB flask, 1,3-cyclohexanedione (5.60 g, 0.05 mol), salicylaldehyde (6.1 mL, 0.05 mol), and urea (0.05 mol, 3.0 g) were dissolved in 20mL ethanol. The contents of the flask are thoroughly stirred after 30 minutes of heating using a magnetic stirrer. Afterwards, a white dust-like residue developed. It has been dried and filtered. To produce pure product, the final prepared sample was recrystallized in hot ethanol. In **Scheme 1**, the production of ligand 2 is shown.



Scheme 1: Synthesis of ligand 1

1-((2,6-dioxocyclohexyl) (2-hydroxyphenyl)methyl)urea (1)

Dust white solid; mw: 276.29; mp:146°C; IR (KBr cm^{-1}) ν_{max}: 3436.28 (-OH), 3076.46 (-NH), 2924.22 (-CH), 1641.32 (-C=O), 1236.77 (-C-N-C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.08 (s, 1H, NH), 7.12-6.90 (m, 4H, Ph-OH), 5.55 (s, 2H,NH_2), 5.32 (d, *J* = 1.7 Hz, 1H, CH-Ph), 5.30 (s, 1H, OH), 4.22 (d, *J* = 6.9 Hz, 1H, CHD), 2.40-1.91 (m, 6H, CHD); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 208.83 (2C, C=O), 162.72 (1C, C=O), 154.0 (1C, C-OH), 130.19, 128.12, 126.50, 121.13, 115.75 (5C, Ar ring), 72.10 (1C, CH), 56.01 (1C, CH), 40.89 (2C, CH_2), 16.57 (1C, CH_2); EI-MS: m/z 277.11 (M^+,16%); Elemental analysis: Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14;%. Found: C, 60.84; H, 5.86; N, 10.12;%.

Antibacterial activity

Antibacterial assessments of the ligand (**1**) and its complexes (**1a-1e**) were experienced in vitro against the bacteria *Escherichia coli*, *Klebsiella pneumaniae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* via Kirby Bauer Disc diffusion technique **[14]**. The antibacterial activity of ciprofloxacin was utilized as a reference. The bacterial cultures were cultivated on petri dishes on nutrient agar medium. The compounds were synthesized in DMSO and immersed in a 5 mm diameter, 1 mm thick filter paper disc. After 24 hours, the width of the inhibitory zone **[15, 16]** surrounding each disc was evaluated for antibacterial activity, and the discs remained put on the already implanted plates and incubated at 37°C. Minimum inhibitory concentrations (MIC) were used to reflect the antibacterial action of ligand (**1**) and its metal complexes (**1a-1e**).

RESULTS AND DISCUSSION

Metal complexes (1a-1e) with ligand (1)

Physical properties

Table 1 shows the physical possessions of the ligand (**1**) as well as the complexes (**1a-1e**) generated from it.

Solubility

The solubility of the ligand (**1**) and the complexes (**1a-1e**) in various solvents was investigated, and the findings are shown

in **Table 2**. The metal complexes (**1a-1e**) derived from ligand (**1**) dissolve more readily in aprotic solvents than in protic solvents, according to solubility experiments **(Table 2)**.

Conductivity measurements

Various solvents, including water, ethanol, chloroform, and DMSO, were used to test the solubility of the newly synthesized metal complexes. The Equiptronics digital conductivity meter (Model EQ-660) was used to determine molar conductance in DMSO, with the cell constant calibrated using 0.1M KCl solution. The electrical conductivity of a 10^{-3} M solutions of respective complexes (2a-2e) in DMSO was determined, revealing the complexes' neutral (non-electrolytic) character. The molar conductance of the mixed ligand complexes (**1a-1e**) of ligand (**1**) ranges from 17 to 26 $\Omega^{-1}mol^{-1}cm^2$. The chloride ions were shown to be coupled to metal ions via conductivity tests, suggesting that they function as ligands rather than ions. Combinations for the produced complexes were allocated based on the metal – ligand ratio (1:2) and the characteristics of the electrolytes as determined by conductance measurements, which aids in describing the structure of the complex. The Conductance properties of metal complexes (**1a-1e**) with ligand (**1**) Were shown in **Table 3**.

NMR Spectra of ligand (1)

The hydrogens of the aromatic rings show a multiplet at 7.12-6.90 ppm in the ^1H NMR spectrum of the Mannich base ligand (**1**) during investigation **(Figure 1)**. The methylene hydrogens linked to the salicylaldehyde and amine hydrogens of the urea show as a peak at 4.22 ppm, whereas the aromatic –OH occurs at 5.30 ppm. The ligand's creation is also determined by the change in a signal equivalent to the secondary amine $–NH_2$ proton of because it was removed in the Mannich process. The carbons of the aromatic rings had peaks at 130.19-115.75 ppm in the ^{13}C NMR spectra of the Mannich base ligand (**1**) in investigation **(Figure 2)**. The presence of a peak at 56.01 ppm shows that the methylene carbon is linked to the salicylaldehyde and urea's amine hydrogens. Furthermore, the carbonyl carbons of the 1,3-cyclohexanedione and urea constituent are represented by the peaks at 208.83 and 162.72 ppm, respectively.

IR Spectra

The existence of a strong band at 3436.28 and 3076.43 cm^{-1}, which would be attributable to the vO-H and N-H groups, is a significant finding in the ligand spectrum **(Figure 3)**. The bands attributable to O-H

and N-H moved towards lower frequency in all the complexes **(Figure 4-8)**, suggesting that oxygen and nitrogen were engaged in coordination between metal ions. In copper complex (**1a**), the M-N bond is represented by the new peak appeared at 855.81 cm^{-1}. The M-O bond is represented by the new peak at 758.11 cm^{-1}. At 493.66 cm^{-1}, there are new bands, which corresponds to the M-Cl bond. The IR Spectral data of complexes (**1a-1e**) and the ligand (**1**) were displayed in **Table 4**.

UV-Visible Spectra

The ligand and complex UV-Visible spectra were measured in the region of 100-1100 nm. The UV spectra of ligand (**1**) primarily revealed two strong maximum bands at 375nm and 200nm, which correspond to the π →π* and n →π* transitions, correspondingly **(Figure 9)**. The Cu (II) complex being investigation has a wide band in the wavelength range of 262 nm, indicating octahedral geometry. Broad peaks at 262 nm and 290 nm were seen in the Ni (II) complex, confirming its octahedral geometry. At 263nm, the location of bands detected for Cr (II) complex displays wide signals, indicating that it has an octahedral geometry. At 258 nm, the Fe (II) complex produced wide signals, confirming its octahedral geometry. The Mn (II) complex emitted wide signals at 262 nm, indicating that it is octahedral. **Figure 10-14** shows the UV spectrums of metal complexes (**1a-1e**).

EPR spectra

The type of metal ligand binding interactions and the arrangement of paired and unpaired electrons may be learned through EPR spectrum analysis. Cu (II) complexes have a unique character in coordination chemistry, with geometries such as tetrahedral, square planar, octahedral, and square pyramidal that may be distinguished by EPR spectroscopy. $g\parallel$, $g\perp$, gavg and G are EPR characteristics that indicate whether the compound is octahedral or tetrahedral. The following criterion confirms the existence of an unpaired electron in the dx^2-y^2 orbital: $g\parallel > g\perp > 2.0023$. For the copper complex, the measured $g\parallel$ and $g\perp$ values are 2.1462 and 2.0131, respectively. The ionic nature is shown by a $g\parallel$ value more than 2.3, while the covalent nature is indicated by a $g\parallel$ value less than 2.3. We can see that the g value (2.1462) is smaller than 2.3, indicating that the compound is covalent. According to Hathaway, G values less than four indicate a significant exchange contact amongst metal centers, whereas G values higher than four indicate a minimal exchange interaction. The G value is 4.76 in this case, thus the

exchange interaction is insignificant. The Cu (II) complex exhibits deformed octahedral geometry, according to the EPR characteristics. The EPR spectra of copper complex (**1a**) was shown in **Figure 15**.

Structure of the Complexes

We recommend the following structure for the complexes (**1a-1e**) produced utilizing the Mannich base ligand (**1**) based on the preceding findings.

Biological screening

Antibacterial activity

The antibacterial assessment of the synthesized ligand (**1**) and complexes (**1a-1e**) were tested. The ligand (**1**) had low activity compared to the corresponding complexes (**1a-1e**). The investigation was done in a controlled environment. In the (**1a-1e**), series, the complex **1b** was only highly active, with an MIC of 2 µg/mL in *S. aureus*. Obviously, the copper complex **1a** was more active against *K. pneumoniae*, with MIC of 4 µg/mL, than the control **Ciprofloxacin**, which had MIC of 8 µg/mL. The manganese complex **1e** was more active against *E. coli*, with MIC of 4 µg/mL, than the control **Ciprofloxacin**, which had MIC of 6 µg/mL. In comparison to complexes (**1a-1e**), complex **1a** (Cu II), complex **1b** (Ni II), and complex **1e** (Mn II), has exceptional activity. Table 5 summarizes the findings.

Table 1: Physical possessions of complexes (1a-1e) and its ligand (1)

Compound	Color	Melting point (^oC)
Ligand (1)	Dust white	146
Copper complex (1a)	Blue	162
Nickel complex (1b)	Pale green	142
Iron complex (1c)	Brown	154
Chromium complex (1d)	Green	160
Manganese complex (1e)	White	172

Table 2: Solubility test results

Compound	Water	Ethanol	Chloroform	DMSO
Ligand (1)	Insoluble	Insoluble	Sparingly soluble	Soluble
Copper complex (1a)	Insoluble	Insoluble	Insoluble	Soluble
Nickel complex (1b)	Insoluble	Insoluble	Insoluble	Soluble
Iron complex (1c)	Insoluble	Insoluble	Insoluble	Soluble
Chromium complex (1d)	Insoluble	Insoluble	Insoluble	Soluble
Manganese complex (1e)	Insoluble	Insoluble	Insoluble	Soluble

Table 3: Conductance properties of metal complexes (1a-1e) with ligand (1)

S. No.	Compounds	Conductance ($\Omega^{-1}mol^{-1}cm^2$)
1.	Copper complex (1a)	17
2.	Nickel complex (1b)	26
3.	Iron complex (1c)	23
4.	Chromium complex (1d)	20
5.	Manganese complex (1e)	21

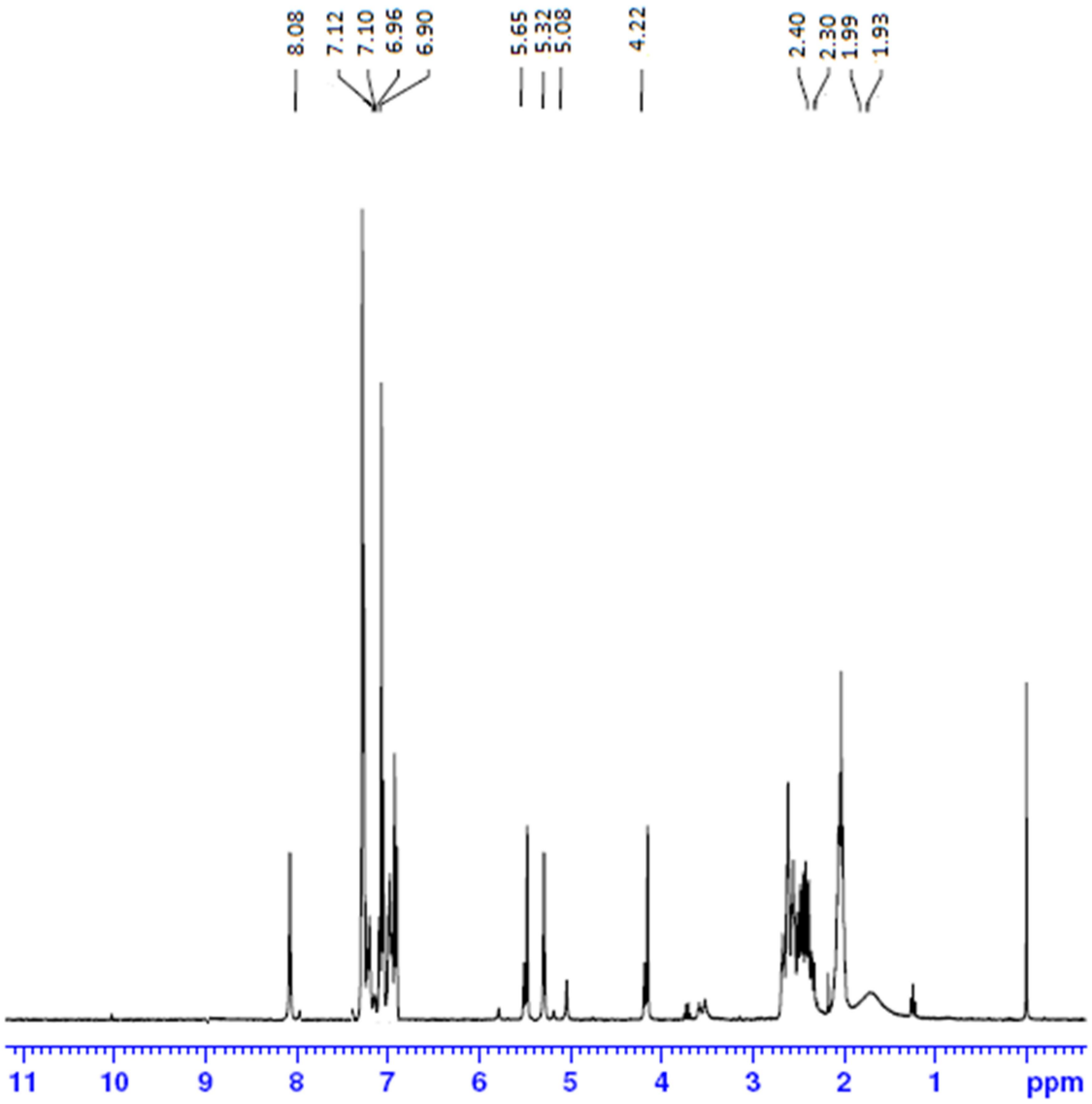


Figure 1: Ligand (1)-^{1}H-NMR spectrum

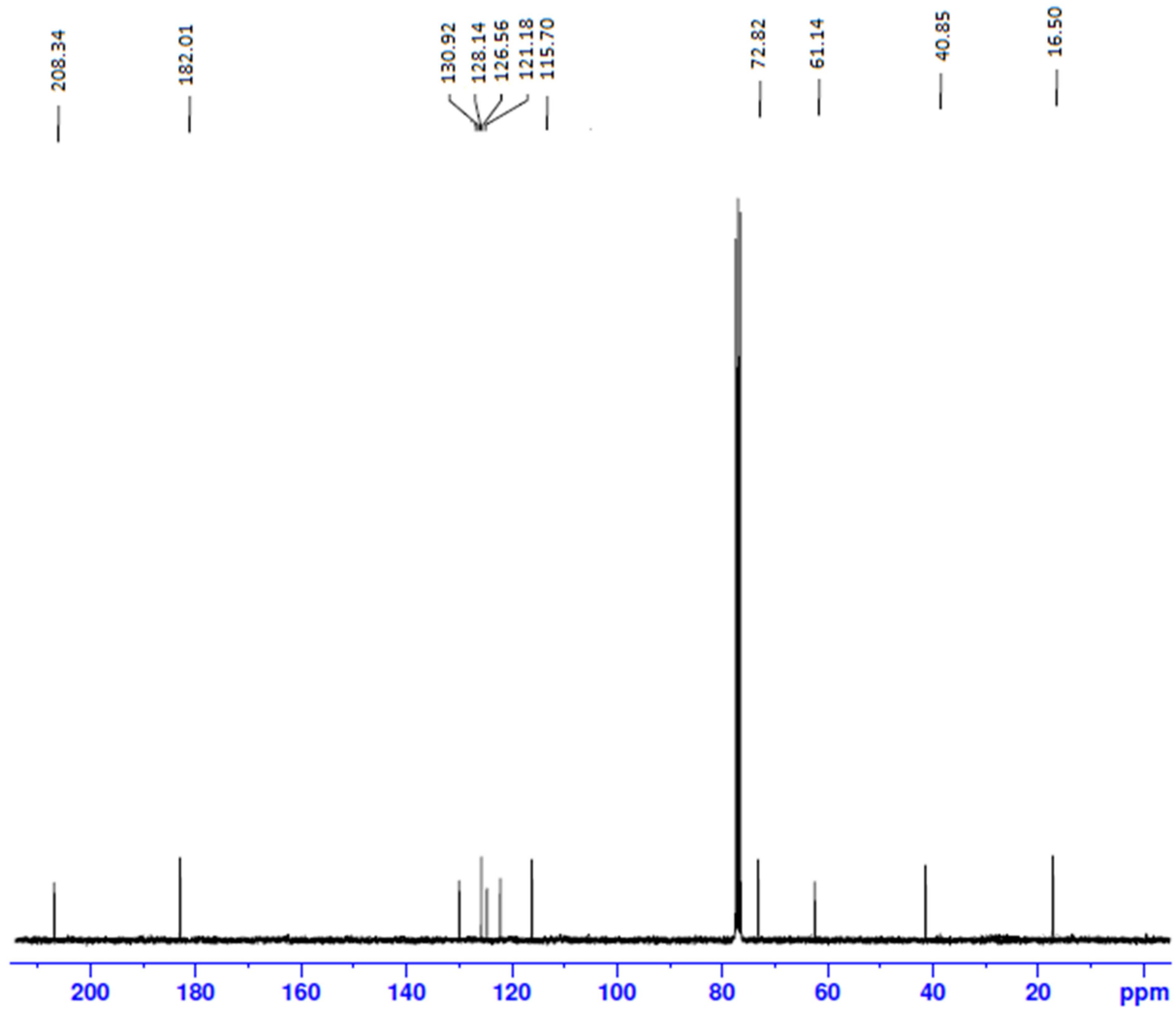


Figure 2: Ligand (1)-^{13}C-NMR spectrum

Table 4: IR Spectral data of complexes (1a-1e) and the ligand (1)

Compound	IR stretching frequency (cm^{-1})				
	-OH	-N-H	M-N	M-O	M-Cl
Ligand (1)	3436.28	3076.46	-	-	-
Copper complex (1a)	3450.43	2950.60	855.81	758.11	493.66
Nickel complex (1b)	3449.65	2950.60	851.78	771.18	493.95
Iron complex (1c)	3440.23	3077.30	854.63	774.91	494.62
Chromium complex (1d)	3450.41	2950.95	854.18	774.95	494.63
Manganese complex (1e)	3429.49	3077.24	853.62	759.76	493.88

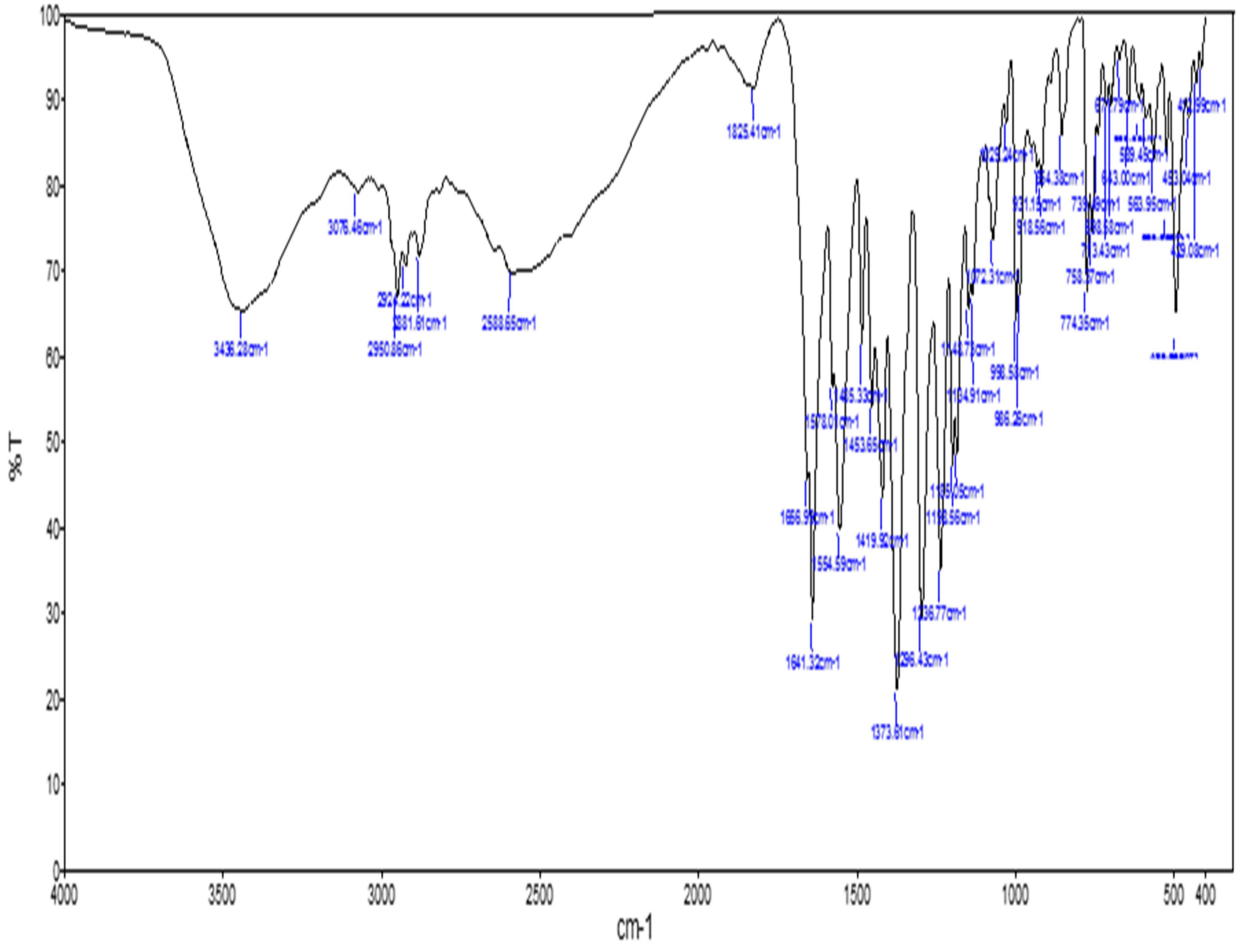


Figure 3: Ligand (1)-FT-IR spectra

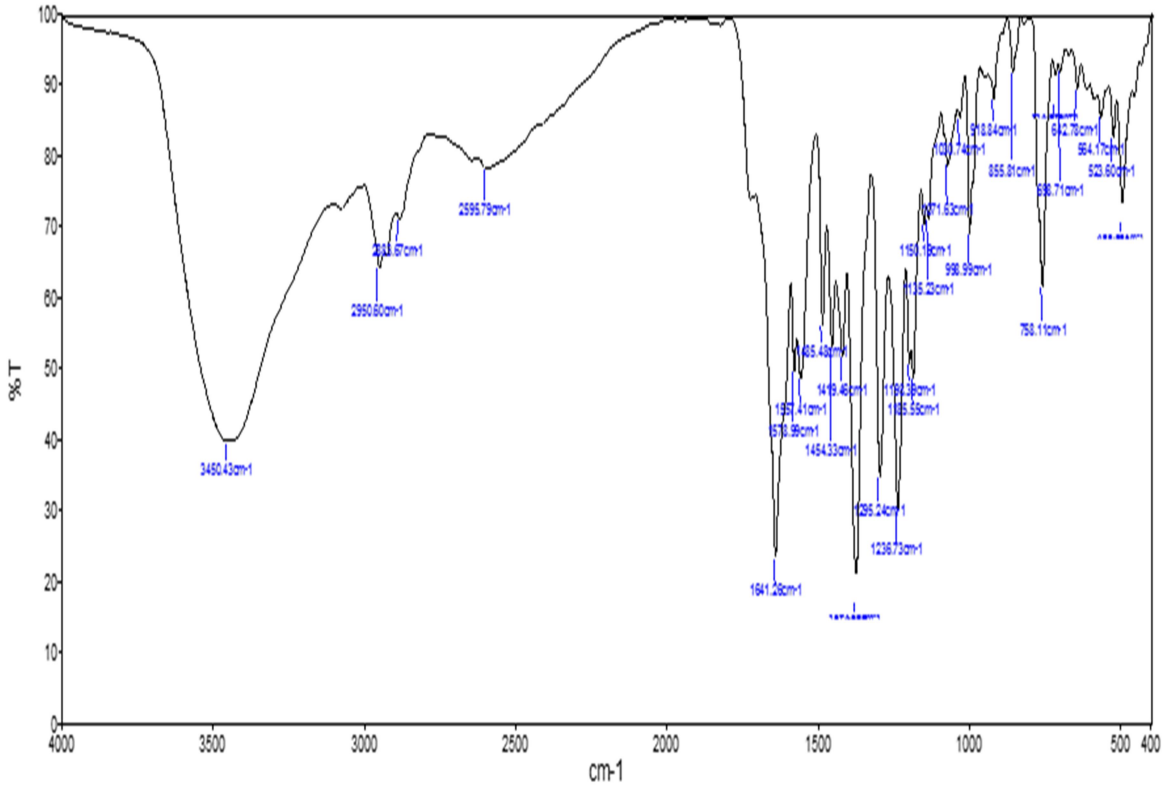


Figure 4: Copper complex (1a)-FT-IR spectra

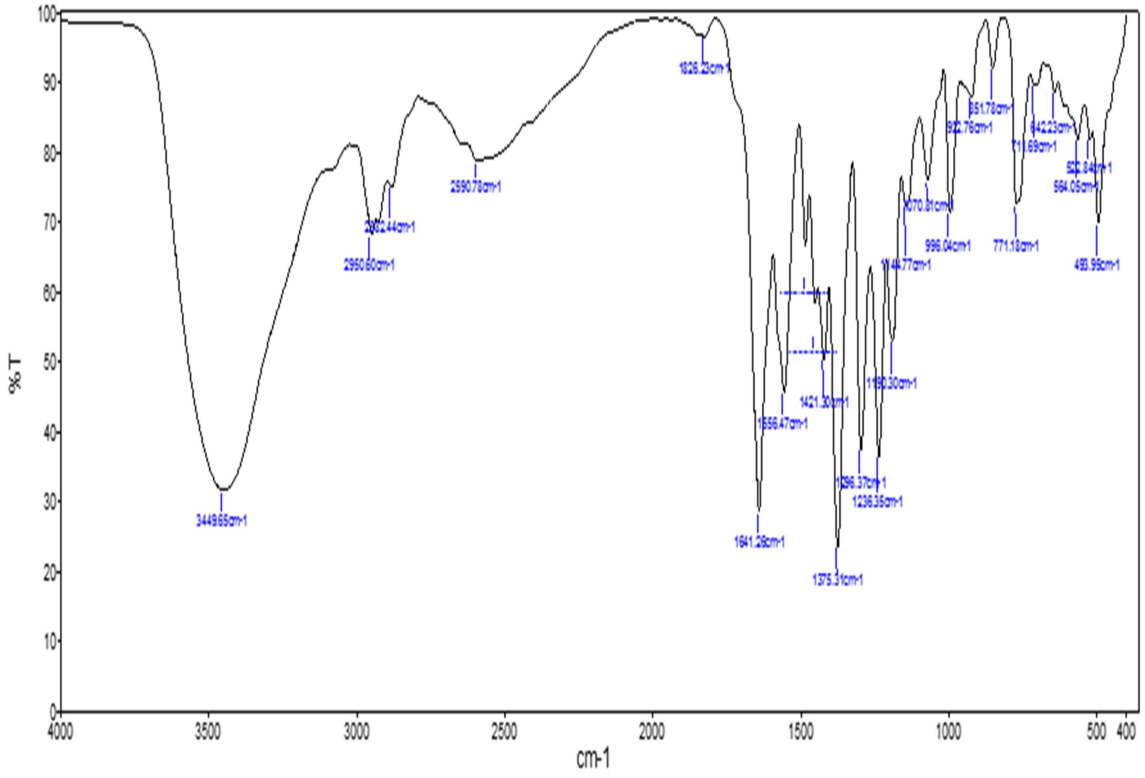


Figure 5: Nickel complex (1b)-FT-IR spectra

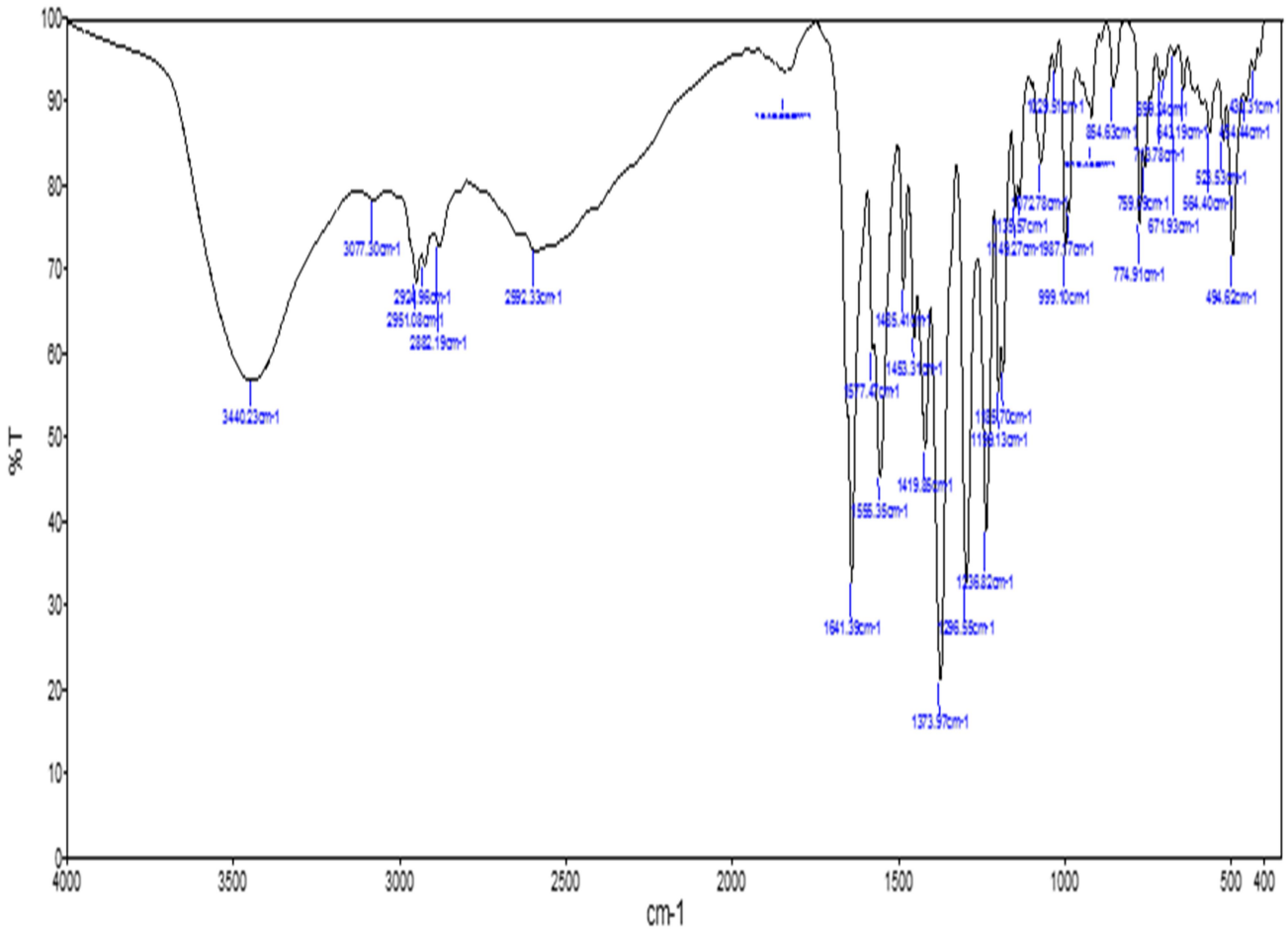


Figure 6: Iron complex (1c)-FT-IR spectra

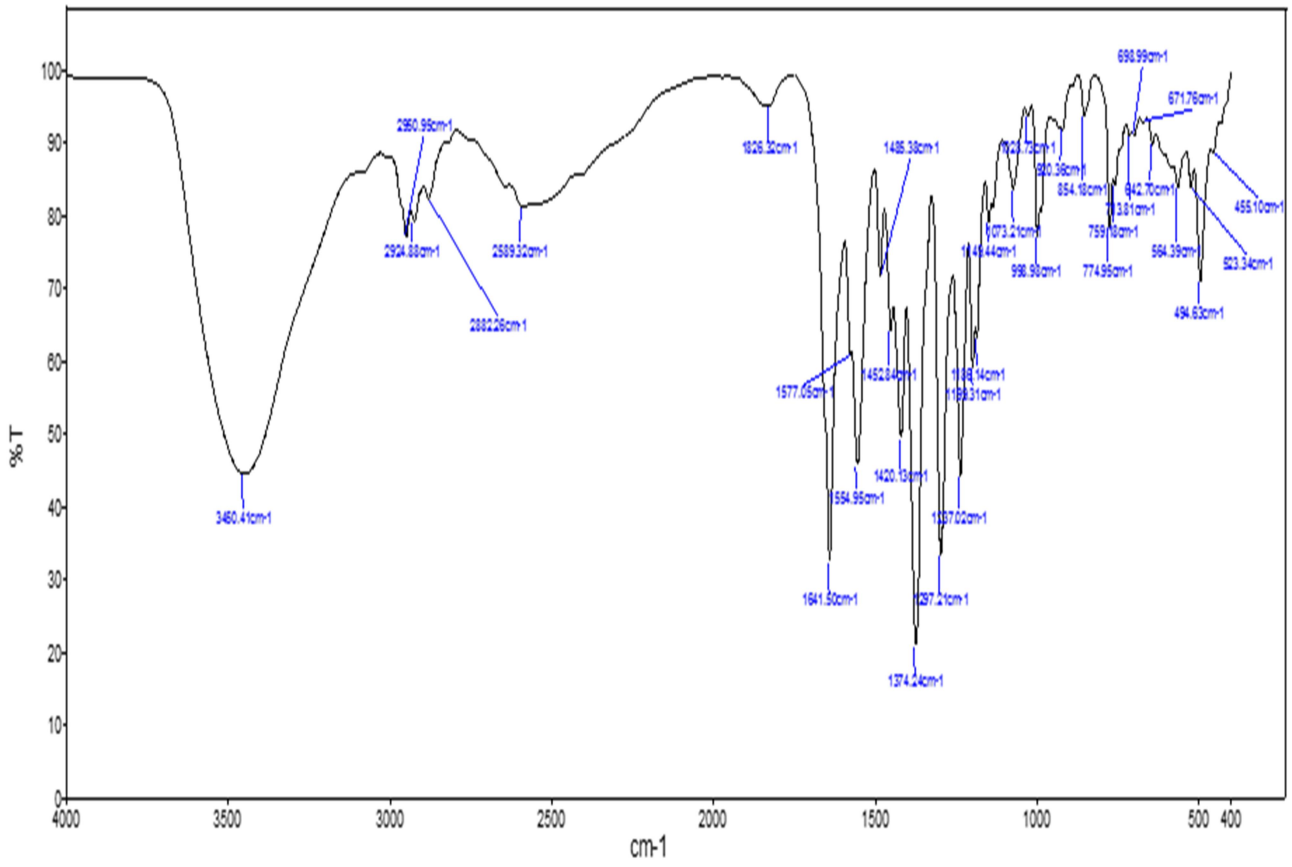


Figure 7: Chromium complex (1d)-FT-IR spectra

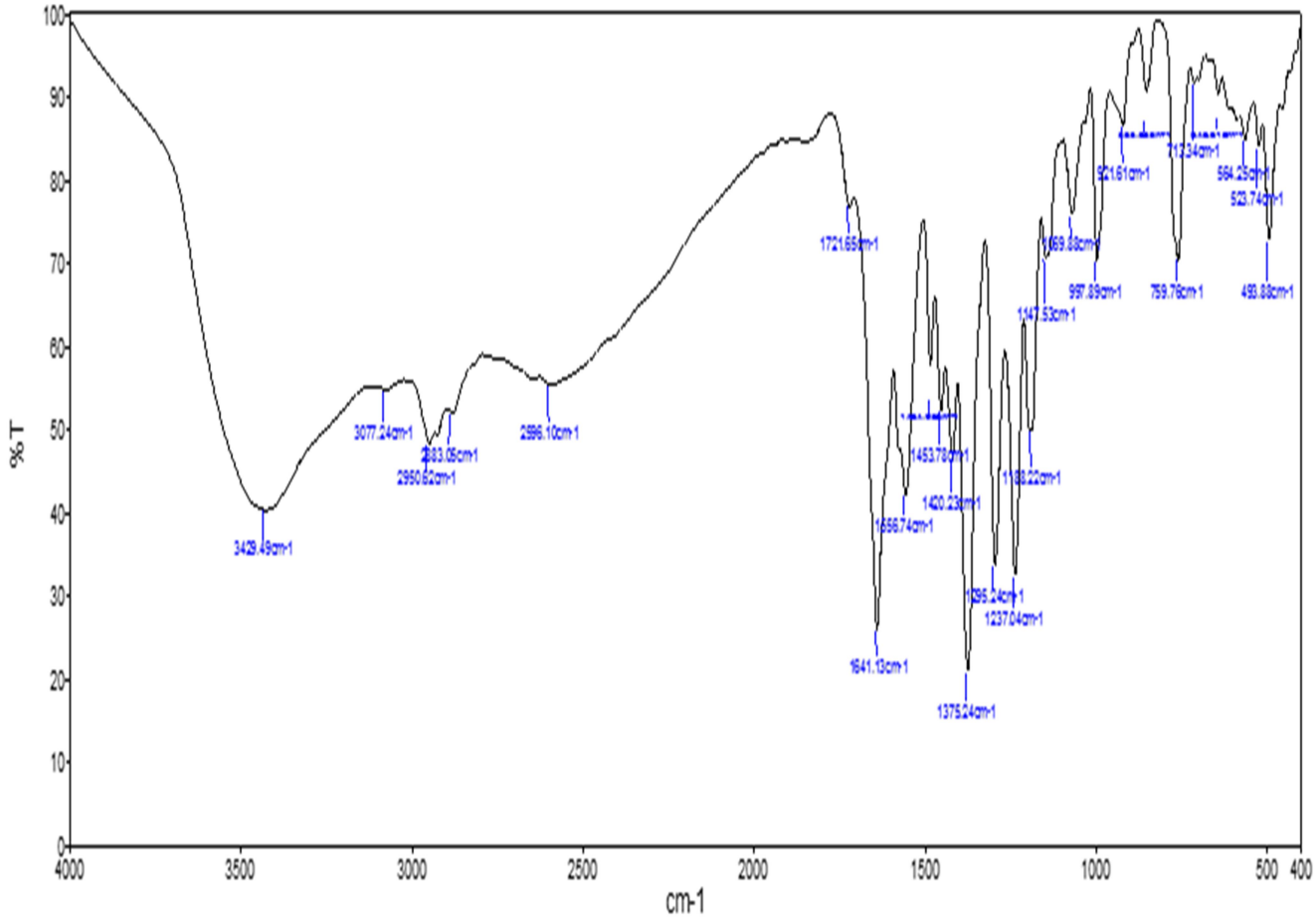


Figure 8: Manganese complex (1e)-FT-IR spectra

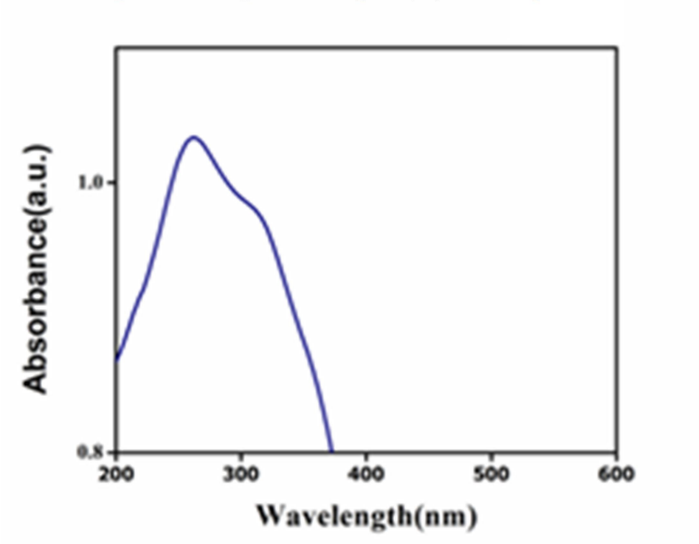


Figure 9: Ligand 1 UV-Spectra

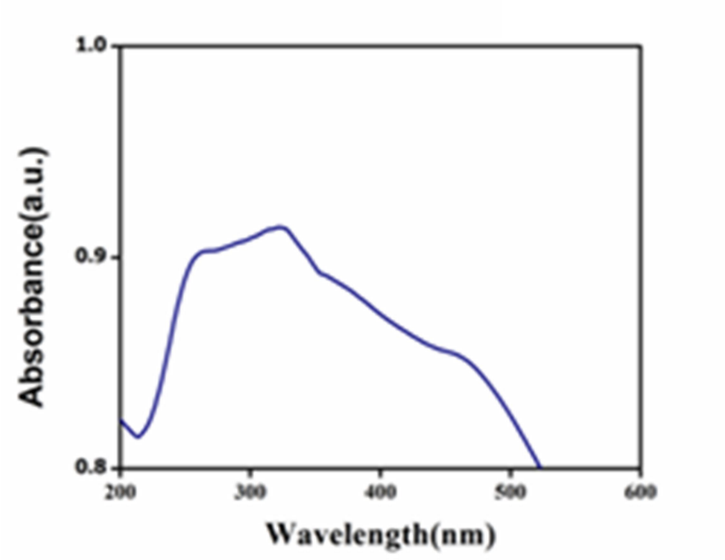


Figure 10: Copper complex (1a) UV-Spectra

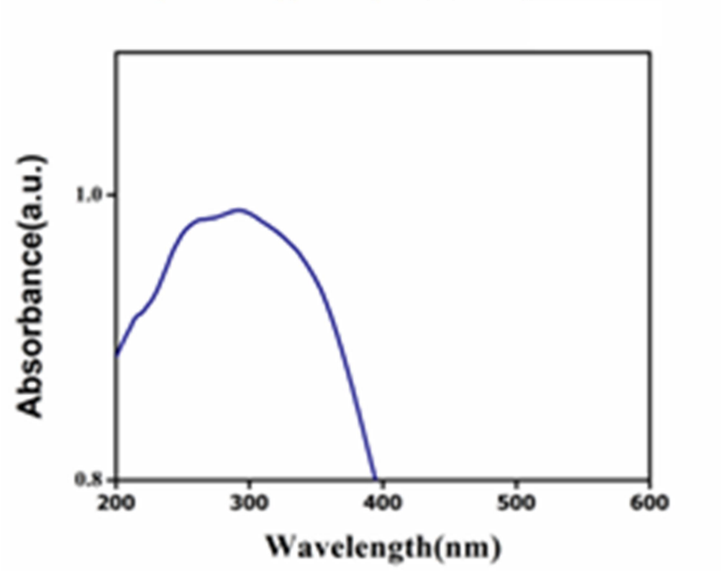


Figure 11: Nickel complex (1b) UV-Spectra

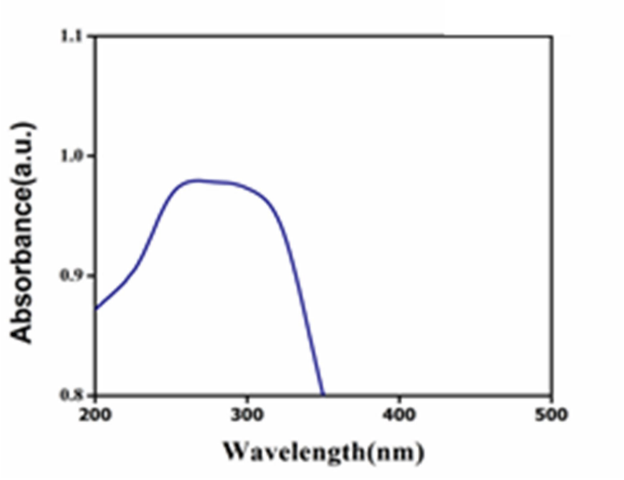


Figure 12: Iron complex (1c) UV-Spectra

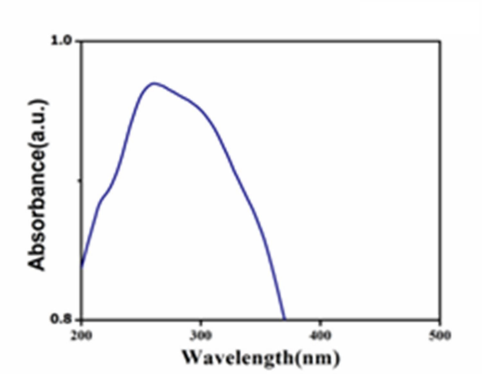


Figure 13: Chromium complex (1d) UV-Spectra

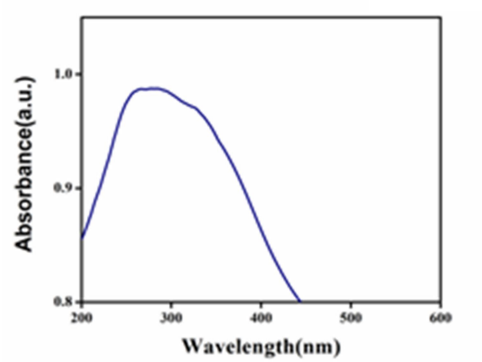


Figure 14: Manganese complex (1e) UV-Spectra

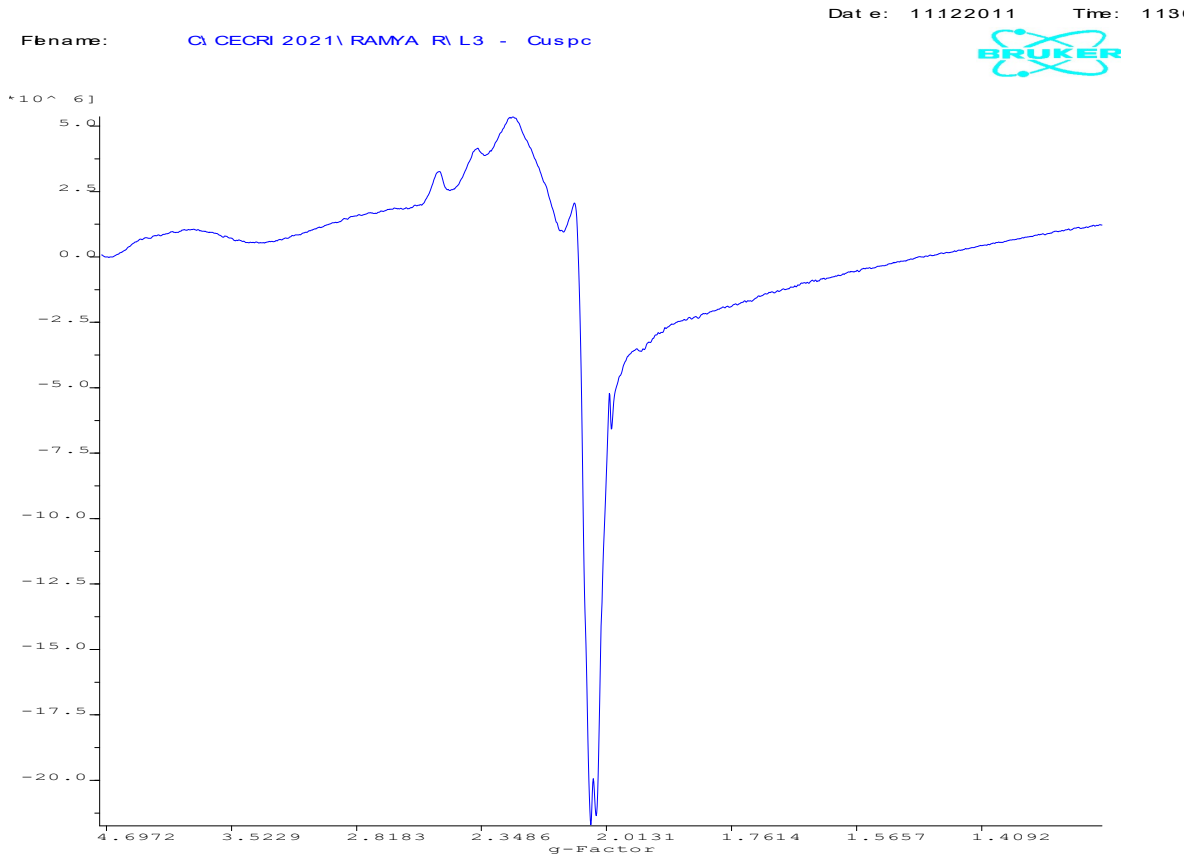
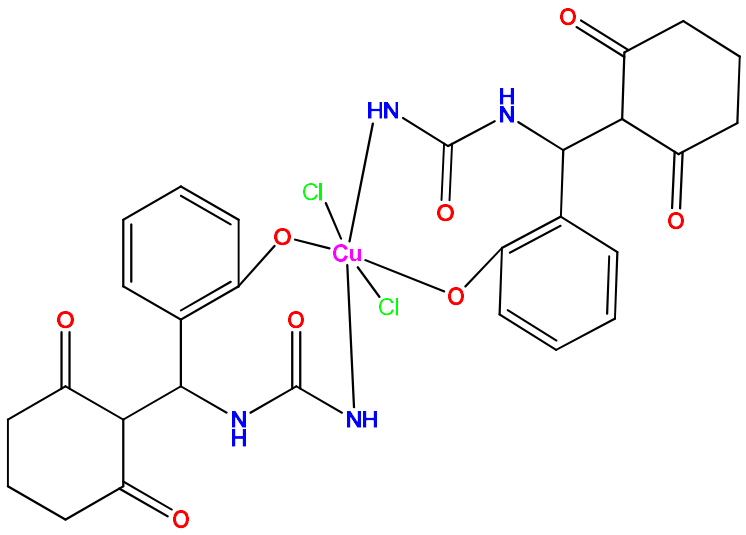
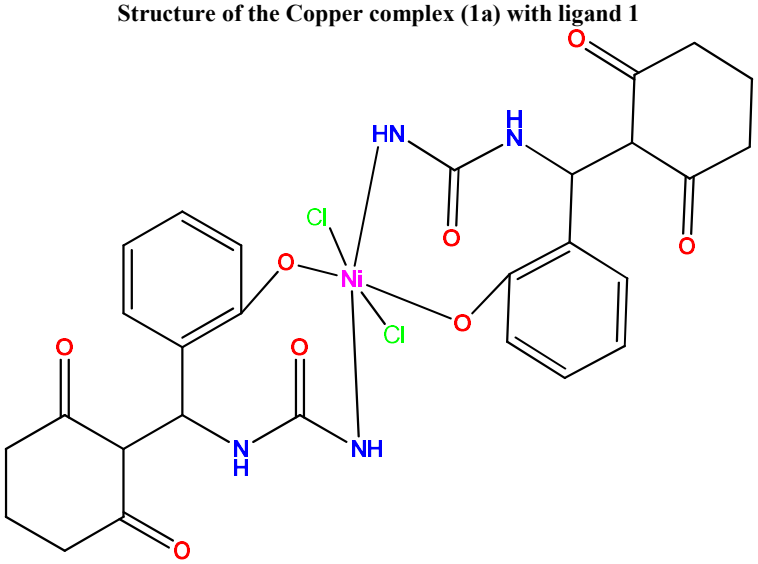


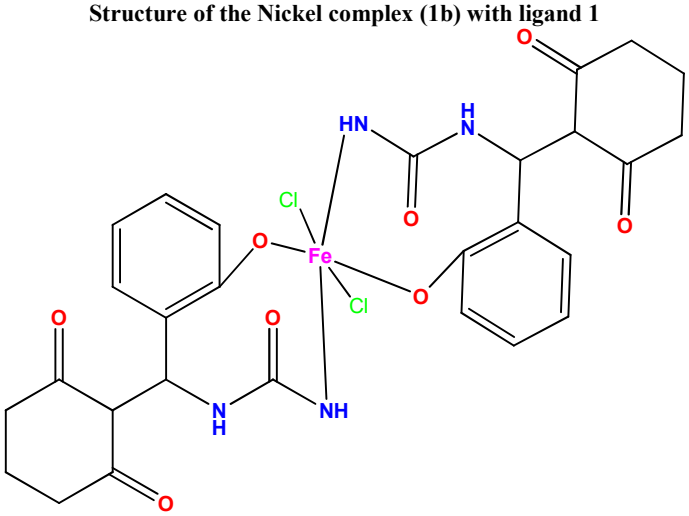
Figure 15: Copper complex (2a) EPR spectra



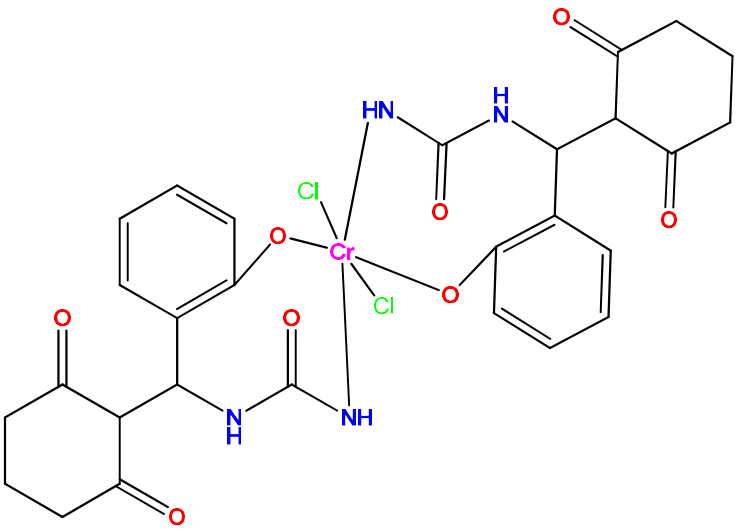
Structure of the Copper complex (1a) with ligand 1



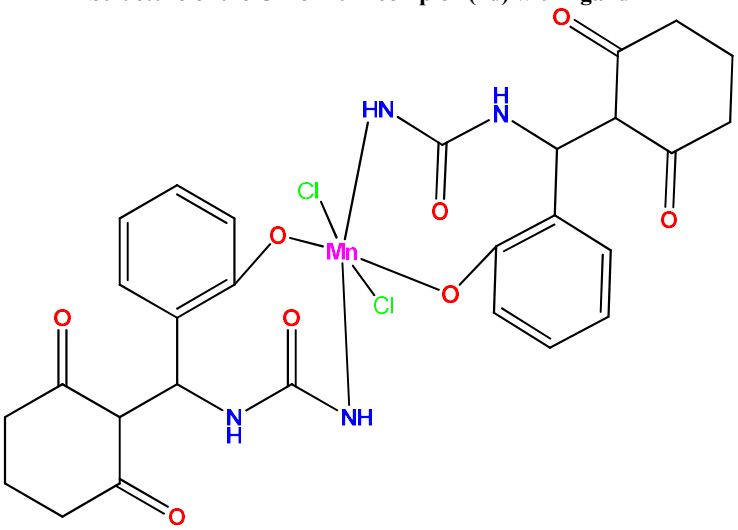
Structure of the Nickel complex (1b) with ligand 1



Structure of the Iron complex (1c) with ligand 1



Structure of the Chromium complex (1d) with ligand 1



Structure of the Manganese complex (1e) with ligand 1

Table 5: Antibacterial assessment of ligand (1) and its complexes (1a-1e)

Compounds	Minimum inhibitory concentration (MIC) in µg/mL			
	S. aureus	*K. pneumaniae*	*E. coli*	*P. aeruginosa*
1	32	16	16	32
1a	8	4	8	8
1b	2	10	10	4
1c	12	14	12	8
1d	6	12	8	4
1e	10	28	4	6
Ciprofloxacin	4	8	6	2

CONCLUSION

The coordination behavior of a Mannich base ligand synthesized from 1,3-cyclohexanedione, salicylaldehyde, and urea is reported in this article. Using the aforementioned Mannich base ligand, Cu(II), Ni(II), Fe(II), Cr(II), and Mn(II) complexes have been produced and described utilizing

analytical and spectroscopic measurements. The Mannich base functions as a neutral bidentate ligand by coordinating to the metal ion via its urea nitrogen and oxygen of salicylaldehyde. The complexes are all octahedral in shape. Antibacterial assessment of the ligand and its metal complexes was tested. The ligand (**1**) and its metal complexes (**1a-1e**) were revealed to exhibit significant antibacterial action against a variety of disease-causing bacteria. The metal complexes revealed to be a more efficient bactericide than ciprofloxacin.

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Conflicts of interest

The authors declare no conflicts of interest.

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Synthesis and characterization of Transition metal complexes with 3-methyl-1H-pyrazol-5(4H)-one and its larvicidal, antifeedant and mosquito larval growth and regulation activities

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Abstract

*Novel one-pot synthesis of transition metal complexes (Cu, Ni, Mn) with bioactive nitrogen containing heterocyclic ligand molecule 3-methyl-1H-pyrazol-5(4H)-one. The synthesized metal complexes (**1a-1c**) were characterized by using spectroscopic techniques UV-Visible and FT-IR. The synthesized complexes (**1a-1c**) were further evaluated for larvicidal activity against 2nd instar southern house mosquito larvae Culexquin quefasciatus and toxicity studies against non-target aquatic species marine fishes of Oreochrombis mossamicus. Complex **1b** was highly active against Culex quinquefasciatus LD_{50} value of 18.52 µg/ml than complexes **1a** and **1c** with the LD_{50} value of 59.97 and 84.73 µg/ml. Complex **1a** showed high toxicity compared with other complexes **1b** and **1c** (Antifeedant activity).*

Keywords: *Metal complexes, Culexquin quefasciatus, Larvicidal activity, Antifeedant activity.*

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Nickel (II) Complexes Synthesis, Characterization and its Larvicidal, and Antifeedant Activities

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Abstract

In this study the synthesis of Nickel complexes with various organic ligands by using ethanol as a solvent. This method offers efficient and mild reaction conditions. The synthesized complexes were characterized by UV- Visible and IR spectroscopy. The synthesized complexes are also evaluated for larvicidal, antifeedant, and mosquito larval growth and regulation activities. Complex **1b** was highly active against *Culexquinquefasciatus*LD_{50} value of 18.52 µg/ml than complexes **1a** and **1c** with the LD_{50} value of 59.97 and 84.73 µg/ml. Among the complexes **1a-1c** the complex **1c** was less active in contradiction of*Culexquinquefasciatus* with the LD_{50} value of 84.73 µg/ml respectively. Complex **1a** exhibited high toxicity associated with former complexes **1b** and **1c**. Complex **1a** produced 80% mortality in 24hr at 100 µg/ml respectively. Toxicity was restrained as death percentage at 24hr. Complex **1b** produced 43% mortality in 24hr at 100 µg/ml. Among the synthesized complexes **1a-1c**the complex **1a** was highly active with the LD_{50} value of 46.08 µg/ml.

Keywords

Nickel complexes, Culexquinquefasciatus, Larvicidal activity, Antifeedant activity.

Introduction

The key division of inorganic chemistry, coordination chemistry, which would be the analysis of the structures, configurations and transformations of complexes produced by ligands coordinated with a transition metal base, can be interrelated with a large portion of inorganic chemistry. In the erection of molecular substances, transition metal complexes play a key role, that show scarce conducting and magnetic properties and find applicability in material chemistry, supramolecular and biochemistry[1-4]. Due to their anticarcinogenic, antibacterial and antifungal properties, nickel (II) complexes of macrocyclic ligands are biologically essential and noteworthy [5]. They have also been checked for their therapeutic properties since they maintain

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Synthesis and Characterization of Copper (II) Complexes with Various Ligands and its Larvicidal, Antifeedant and Mosquito Larval Growth and Regulation Activities

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Abstract

The catalyst free one-pot synthesis of Copper complexes with various organic ligands by using ethanol as a solvent. This method offers efficient and mild reaction conditions. The synthesized complexes were described by UV- Visible and FT-IR spectroscopy.The synthesized complexes are also evaluated for larvicidal, antifeedant, and mosquito larval growth and regulation activities. Complex**1b** was highly active against Culexquin quefasciatusthan complexes **1a**and **1c**with the LD_{50} value of 45.28 µg/mL. The complexess **1a**and **1c**were less active against Culexquin quefasciatus with the LD_{50} values of 69.83 and 84.73 µg/ml respectively. Complex **1a** produced 66% mortality in 24hr at 100 µg/ml againstOreochromis mossambicus in antifeedantscreening and also toxicity was measured as death percentage at 24hr. Complex **1b** produced 60% mortality in 24hr at 100 µg/ml. Among the synthesized complexes **1a-1c** the complex **1a** havinghightoxicity with the LD_{50} value of 69.57 µg/ml.

Keywords: Copper complexes, Culexquin quefasciatus, Larvicidal activity, Antifeedant activity.

Introduction

Copper displayssignificant biological action whichever as acrucialdrop metal or as a fundamental of numerousexogenously directedmixes in individuals. Theearliercharacterof copper was destined to albumin, ceruloplasmin, and also formerproteins, whereas in later it is assured to various types of ligands for complex formation that interrelate with biomolecules,mostlynucleic acids and proteins. The multidimensionalcharacter of copper in bioticorganisms is validated by more than a fewstudies. In precise the contribution of copper in humanoidinfections has been defined from a remedial-chemical [1]and a biochemical view [2] concentrating on the molecular functioning of Cu conveyance [3].Overexistinginvestigationexertion is mentioned on copper homeostasis [4] and its kin to ironmetabolism [5] in addition to the part of copper in naturalproceduresinterrelated to human pathology and physiology [6, 7].

Copper (II) complexes have a critical function in the active sites of many metalloenzymes in live creatures and have the potential to be used in a wide range of catalytic processes in live organisms, including electron transfer processes and the stimulation of certain anticancer compounds [8]. Bioinorganic [9] and medicinal chemistry [10] both use the above-mentioned advancements. Furthermore, copper (II) chelates were developed to interact with biological