وزاره التعليم العالي والبحث العلمي جامعه ديالى
كليه تربيه للعلوم الصرفة
قسم الكيمياء

تحضير, تشخيص و الفعالية البايولوجية لبعض المعقدات الفلزية الجديدة المتضمنة مشتقات الثايوسيميكاربزايد و السيميكاربزايد

رساله مقدمة الى مجلس كلية التربية للعلوم الصرفة جامعه ديالى

وهي جزء من متطلبات نيل درجة الماجستير فـي علوم الكيمياء

من قبل الطالبة

ايمان احمد كاظم

بكالوريوس تربية علوم كيمياء/ جامعة ديالى (٢٠١٦م)

باشراف

أ.م.د نصري جاسم حسين

أ.د سيتي فيروزه محمد يوسف

٢٠٢٤ م ١٤٤٦ هـ

Ministry of Higher Education and Scientific Research
University of Diyala
College of Education for Pure Science
Department of Chemistry

Synthesis, Characterization and Antibacterial Activity of some New Metal Complexes Containing Thiosemicarbazide and Semicarbazide Derivative

A Thesis

Submitted to Council of the College of Education for Pure Science, University of Diyala in partial fulfillment of the requirements for the degree Master of Science in Chemistry

By

Eman Ahmed Kadhim

B.Sc. Chemistry Science 2016

Supervised By

Assist. Prof. (Ph.D.)Nasry Jassim Hussien
Prof. (Ph.D.) Siti Fairus Mohd Yusoff

2024 A.D **1446 A.H**

Abstract

This study presents the synthesis and characterization of two new thiosemicarbazide and semicarbazide ligands of N^1-cyclohexyl-N^2-(dimethylcarbamoyl)hydrazine-1,2-bis(carbothioamide) (L^1). and N-cyclohexyl-2-((dimethylcarbamoyl)carbamothioyl)hydrazine-1-carboxamid (L^2). Two -step synthetic procedures were used to obtain the previously mentioned ligands. The first step included preparing the starting materials, N_cyclohexylhydrazine carbothioamide for L^1 and N_Cyclohexylhydrazine carboxamide for L^2. The second step included the reaction of ammonium thiocyanate with dimethyl carbamoyl chloride using the solvent methanol, and a filtrate was obtained from this step, after which The starting material mentioned in the first step was mixed with the filtrate of the second step and the mentioned ligands were obtained The general formula of the ligands is;

$[MCl_2(H_2O)(L^1)]$;$[MCl_2(H_2O)(L^2)]$ Where **M**=(Mn^{+2},Co^{+2},Ni^{+2},Cu^{+2}) All the mentioned ligands were characterized using Mass spectroscopy, UV-Vis, NMR (^1H and ^{13}C) A number of transition element complexes were prepared and characterized by reacting the aforementioned ligands with chlorides of metal ions, Mn^{+2}, Co^{+2}, Ni^{+2}, Cu^{+2}, , where a metal:ligand reaction was performed in a 1:1 mole ratio using the solvent methanol to obtain the complexes the following formula;

$[MnCl_2(H_2O)(L^1)]C_1$,$[CoCl_2(H_2O)(L^1)]C_2$,$[NiCl_2(H_2O)(L^1)]C_3$,$[CuCl2(H_2O)(L^1)]C_4$, $[MnCl_2(H_2O)(L^2)]C_5$,$[CoCl_2(H_2O)(L^2)]C_6$, $[NiCl_2(H_2O)(L^2)]C_7$, $[CuCl_2(H_2O)(L^2)]C_8$,

and all the prepared complexes were also characterized using FT_IR, UV_Vis, elemental analysis (C.H.N.), measurement of molar conductivity, melting points, and magnetic susceptibility measurements. Measurements of the molar

CHAPTER ONE

Introduction

1.1 Introduction

The study of metal complexes and their behavior is known as coordination chemistry. The term "complex" refers to collections of ions or particles that can cohabit but are more comfortable when bound together in a predetermined pattern. The chemistry of structured arrangements is the primary emphasis of coordination chemistry. The study of coordination compounds takes up a significant percentage of modern inorganic research, which proves that many coordination compounds are versatile and helpful. Their relevance and usefulness are continually being viewed from new angles. These compounds are structurally diverse but have amazing reactivity, analytical uses, and catalytic effects. Additionally, they are essential in many biological activities [1]. Semicarbazides and thiosemicarbazide derivatives are well-known as potent Tuberculosis pharmacophores [2-4] Various biological functions, including effects on cell membranes that are anti-cancer, anti-human Immunodeficiency Virus Test, anti-bacterial, anti-viral, and anti-microbial, are exhibited by semicarbazides, thiosemicarbazides, and their derivatives. In addition to their role in controlling plant growth, they can also diffuse across semi-permeable barriers [5]. By reacting certain ketones or aldehydes with semicarbazides, important compounds like thiosemicarbazones and semicarbazones can be created Thiosemicarbazones are generated when sulfur atoms are substituted for oxygen atoms in semicarbazones. When these thiosemicarbazones come into contact with metallic cations, they create complexes and chelating ligands [6]. Thiosemicarbazide is the traditional bioisostere of semicarbazide, where sulfur replaces oxygen in the chemical structure NH_2-NH-(C=O)-NH_2 [7] Semicarbazide and thiosemicarbazide are frequently found in the chemical structures of medically important compounds. They play a crucial role in the drug design process because they can create hydrogen bonds, which are regarded as key interactions between drugs and biological targets [8]. There has

been a lot of focus on thiosemicarbazide and its derivatives due to their pharmacological characteristics. The antitumor action of thiosemicarbazide complexes is very diverse. Analytical reagents for metal (II) ion separations are another area of current interest for thiosemicarbazide derivatives [9]. Furthermore, thiosemicarbazone derivatives are deemed indispensable owing to their broad-ranging pharmacological effects. They provide analgesic and antiallergic properties and are utilized in the development of medications to treat bacterial infections and disorders of the central nervous system. These derivatives play a critical role in the synthesis of bioactive and pharmaceutical substances, thereby contributing significantly to the field of medicinal chemistry. Furthermore, thiosemicarbazones have found applications in various fields of chemistry, including dyes, photographic films, plastics, and textiles, among others. As time has passed, these compounds have demonstrated an array of biological activities, such as antimicrobial properties [7]. Scientists have made great strides in the field of chemistry, particularly in the study of coordination, by verifying numerous industrial ways to improve the production and stability of these molecules [10]. These substances are noteworthy due to their interaction with transition metals as chelating agents [11]. Antiviral properties are one of the bioactivities exhibited by ligands generated from semicarbazide [12]. Thiosemicarbazone and semi-carbazide are useful for coordinating metal ions and controlling cell entrance rates due to their specific characteristics. Researchers have the opportunity to explore different biological systems and create innovative treatments by taking advantage of their capabilities. [13]. The amazing ligating characteristics of thiosemicarbazide and semicarbazide compounds have been highlighted by numerous researchers recently. Hence, they bind to metal centers by bridge mode, bi-dentate type, or mono. It was shown that these chemicals may protect different metals against acidic corrosion [14]. Experimental evidence suggests that metal complexes of

thiosemicarbazones provide superior bioactivity and protective profiles compared to free ligands [15]. The study of chemical reactions in different organic molecules is a highly prominent branch of organic chemistry. Industrial and periodic chemists find these compounds significant for a variety of reasons, and they keep giving researchers new molecules to work with [16, 17].

1.2 Semicarbazide

Semicarbazide is a chemical compound with the formula $OC(NH_2)$ (N_2H_3). It is a water-soluble white solid [18]. Semicarbazide is considered a raw material, and semicarbazide is formed by reacting urea with hydrazine as follows; [19]

$$OC(NH_2)_2 + N_2H_4 \rightarrow OC(NH_2)(N_2H_3) + NH_3$$

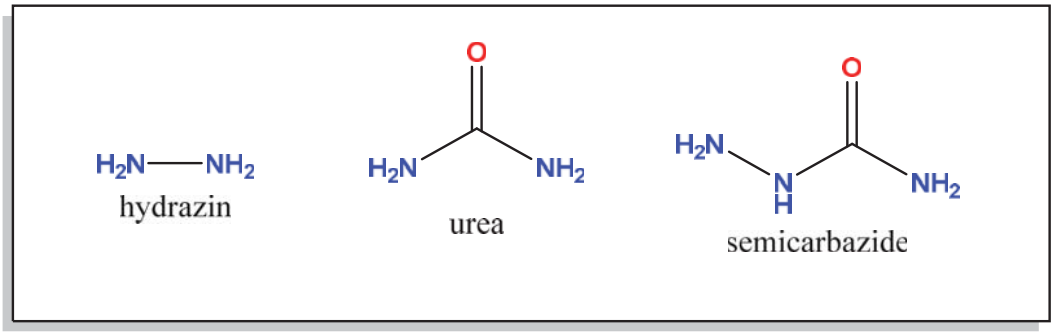


Figure (1-1) :Structure Urea, Hydrazine, Semicarbazide

Semicarbazide is a urea-based monocarboxylic acid amide that has one of its amino groups substituted with hydrazine. It is a one-carbon molecule belonging to the urea family, and a carbohydrazide. Semicarbazide / Thiosemicarbazide The simplest hydrazine derivative of thiocarbamic acid is thiosemicarbazide (NH_2-NH-$CSNH_2$) as in the figure(1-1) [20]. Toxic semicarbazide is a byproduct of nitrofurazone, a veterinary medicine that is no longer used. While nitrofurazone is one of the many sources of semicarbazide in aquatic goods, it is by no means the sole one. In addition to this, it can also be created by contaminating raw resin ingredients [21]. Semicarbazide, alternatively referred

to as carbamoyl hydrazine, was an intermediate in the synthesis of prednisone and adrenobazone [22, 23] and was utilized as a photochromic dye in thermal recording paper. Thiosemicarbazide and semicarbazide are organic compounds that contain sulfur, oxygen, or nitrogen, and exhibit a wide range of biological activities. Schiff's bases are chemical compounds that are generated through the condensation of aldehydes or ketones with various amines [5]. A minor byproduct of the high-temperature decomposition of azodicarbonamide was semicarbazide [24, 25]. A through the semicarbazide is an imine derivative in organic chemistry that is produced condensation of a ketone or aldehyde with semicarbazide. Because they are produced by reacting an aldehyde or ketone with the terminal $-NH_2$ group of semicarbazide, which exhibits similar properties to primary amines, they are categorized as imine derivatives. Semi-carbazones, also known as hydrazine carbonamides, belong to a class of organic compounds that exhibit significant biological activity. Their products are particularly well-known due to their versatile biological and medical functions. They serve as virtuous intermediates in the production of pharmaceutical and medicinal substances and are, as such, frequently used in the field of therapeutic chemistry. Additionally, they are commercially utilized as colorants, photographic films, and textile polymers [26, 27]. The chemical behavior of thiosemicarbazide is similar to that of its semicarbazide counterpart; however, the thione group has greater chemical flexibility than the keto group, which allows for a more diversified behavior of thiosemicarbazide [28]. The use of these derivatives in chemical synthesis has become a standard method for preparing a diverse variety of heterocyclic compounds [29]. In recent years, there has been a lot of research on the synthesis and characterization of transition metal complexes with semicarbazide and thiosemicarbazone [30, 31]. The creation of transition metal complexes, in which the Lewis acid is coordinated via hetero atoms with unbound lone pairs of electrons, has greatly

enhanced chelating chemistry. Metal complexes with Lewis bases comprising nitrogen, sulfur, and phosphorous donors have been shown to have potential pharmacological actions [32, 33]. Semicarbazone and thiosemicarbazone ligands often coordinate with transition metals via their oxygen, nitrogen, and sulfur donor atoms in (N, S) bidentate or (N, N, S or O, N, S) tridentate forms to create metallic complexes [19, 34]. They typically operate as chelating ligands, with donor imine groups reacting with transition metal empty d-orbitals to form complexes. Complexes can have bioactivities that free ligands do not show [35]. According to the IUPAC recommendations for the nomenclature of organic compounds [36], derivatives of semicarbazide of the types: R-CH N-NH-CX-NH_2 and R_1 R_2 C-N-NH-CX-NH_2, which are usually obtained by condensation of semicarbazide with suitable aldehydes and ketones, may be named by adding the class name'semicarbazone (X=O) or 'thiosemicarbazone' (X=S) after the name of the condensed aldehyde RCHO or ketone R. Derivatives with substituents on the amide or thioamide nitrogen, R_1 R_2C=N NH CX NR_3R_4 on the X atom, R_1 R_2 C=N N=CXR_3 NH_2 are also commonly included in this class. R_1R_2C = N NR_3 C X NH_2 (R=alkyl These kinds of chemicals often react with metallic cations, producing complexes in which SCs and TSCs function as chelating ligands. The number of these complexes has progressively expanded over many years [37]. Metal complexes have been useful in drug development and medicinal chemistry [38, 39]. The d-orbitals of transition metals are not filled and their oxidation states can change. Transition metals, sometimes known as d-block elements, include copper, cobalt, nickel, palladium, and silver. The metals play a crucial role in biological redox processes due to their relative stability in different oxidation states [40]. The broad reactivity of transition metal catalysts has led to their widespread use as valuable tools in modern synthetic organic chemistry, permitting a variety of chemical transformations [41]. In thin-layer chromatography, semicarbazide is utilized as a detection

reagent (TLC). Under ultraviolet light, the α-keto acids stained by semicarbazide on the TLC plate may be seen as semicarbazones and thiosemicarbazones have garnered a lot of attention from scientists in the chemical and biological sciences [42], antiviral and antimalarial [19], and cellular metal-binding [43] activity Since the synthesis of semicarbazide complexes was required for the treatment of several illnesses, there has been an upsurge in research into their manufacture and investigation due to the promising biological effects of semicarbazide and their derivatives of transition metal complexes.

1.3 Thiosemicarbazide

Thiosemicarbazide is a chemical compound with the formula $H_2NC(S)NHNH_2$. A white, odorless solid, it is related to thiourea ($H_2NC(S)NH_2$) by the insertion of an NH center. They are commonly used as ligands for transition metals as in the figure (1-2) [44]

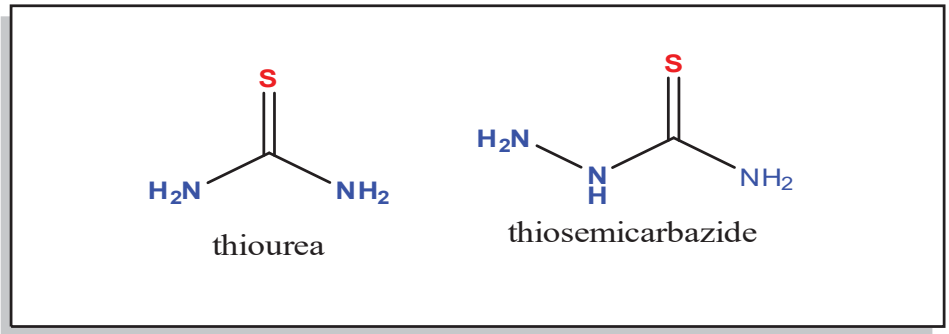


Figure (1-2) :Structure Thiourea, Thiosemicarbazide,

One notable hydrazine derivative of thiocarbamic acid is thiosemicarbazides also known as NH_2-NH-$CSNH_2$ (hydrazine c as arbothiomidic). thiosemicarbazide and semicarbazide have similar chemical behaviors, however, thiosemicarbazide's thiol group is more versatile and adaptable than semicarbazide's ketone group [45]. In organic chemistry, thiosemicarbazide is a beneficial compound because it has a sulfur atom in place of one amino group and a central semicarbazide moiety (-C(=O)$NHNH_2$) [17]. Thiosemicarbazide

utilizes the sulfur atom as the donor atom. Compounds containing C=S are capable of forming cluster compounds that are linear, two-core, or three-dimensional. Additionally, they can merge elements individually or between two or more elements to form highly coordinated polymers. Prominent donor groups, such as "ONS, ONO, NNO, and NNS," demonstrate multifaceted coordination behaviors by functioning as monomers when an element is attached to a ligand or two ligands. Furthermore, thiosemicarbazide dimers (diodes) can be formed when thiols link the central atom [46, 47]. The pharmaceutical and chemical industries rely heavily on thiourea derivatives and thiosemicarbazide [48, 49]. Recent scientific research has revealed that thiosemicarbazides, an organic compound class, may have the capacity to affect various mechanisms implicated in tumor development. Their effect on angiogenesis and critical enzymes associated with tumorigenesis, including topoisomerases, ATP-ases, and dihydroorthane dehydrogenase, has been demonstrated by research. Moreover, thiosemicarbazide-derived compounds demonstrate the capacity to stimulate apoptosis in neoplastic cells and manifest antioxidant and anti-inflammatory properties [50]. Besides that, chelation with metals significantly influences thiosemicarbazide biological behavior [51]. Researchers have recently shown a renewed interest in thiosemicarbazide compounds and their complexes, recognizing their wide range of applications in pharmacology. These applications include antivirals [52], antifungals [53,54], , tuberculosis agents [55, 56], and Human Immunodeficiency Virus drugs [57]. They are DNA inhibitors, which makes them useful as antivirals [58]. TSC is a synthetic compound that can be chemically modified to yield novel compounds with improved biological properties. Several TSC derivatives have been synthesized and tested against various pathogens [59, 60]. TSC has antifungal, antibacterial, antioxidant, and anti-tumor properties [61, 62]. TSC demonstrated positive results as an antifungal drug against Paracoccidioides spp [60] and Candida spp

[59]. TSC derivatives meet critical criteria for new drug development, such as low toxicity, affordability, and strong antimicrobial activity. Despite TSC's in vitro biological activities, its potential as a drug may be [63]. reduced in vivo due to degradation by physiological enzymes Nanostructured drug delivery systems are ideal for preserving the integrity of thiosemicarbazone in vivo applications. These systems have been extensively used in various in vivo scenarios, including enhancing the oral bioavailability of antifungal amphotericin B [64] and increasing the intestinal permeability of itraconazole [65]. Furthermore, they contribute to cancer diagnosis and prognosis [66, 67]. It is also used in the treatment of brain tumors [68]. Thiosemicarbazones have thione thiol tautomerism, which allows them to bind to metal ions in either anionic thiolate or neutral thione forms [69]. Thiosemicarbazones exist in the solid state of thione [69, 70], but in solution, they tend to tautomerize into thiols. These compounds function as bidentate ligands, coordinating via azomethine nitrogen and thione/thiolate sulfur. Ligands can adopt a tridentate coordination mode in the presence of nearby coordination functionality. [71, 72]. Heterocyclic thiosemicarbazones and their metal complexes continue to be of great interest. Interestingly, in some cases, biological activities increase following metal complexation rather than with the parent ligand alone. Depending on the aldehyde or ketone used in thiosemicarbazone synthesis, they can act as unidentate, bidentate, or multidentate chelating agents when forming complexes with metal ions. Thiosemicarbazone analogs are especially important, particularly those with diverse biological and pharmacological activities. These compounds are critical intermediates in developing pharmaceutical and bioactive materials, with numerous applications in medicinal chemistry. The imine bond in these compounds is beneficial for organic synthesis, especially in forming heterocycles and non-natural β-amino acids [73, 75], antitumor [76, 78], anti-inflammatory, and anti-amoebic properties are among the many activities

associated with thiosemicarbazide [79, 80]. Further, antibacterial properties have been observed in these compounds [81, 82]. The diverse biological activities of TSCs and their metal complexes have prompted extensive research [83, 84]. In its early 20th century applications, these substances were utilized as antituberculosis and leprosy agents [70, 85]. Recent applications for thiosemicarbazones as antiviral agents include the treatment of smallpox [84]. In pursuit of developing these substances as anticarcinogenic agents in clinical phase II trials for various cancer types, researchers have broadened their inquiries to include antitumor properties [86, 87]. TSCs are also utilized in optical storage devices, telecommunications, and spectrophotometric metal determination. It is worth mentioning that TSCs can be found in two forms: tautomeric thione (A) and thiol (B) as in the figure (1-3) [88, 89].

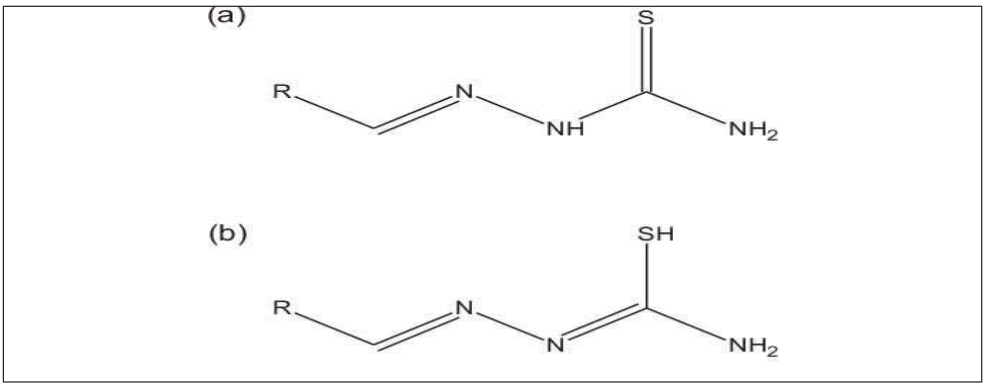


Figure (1-3) : Thiosemicarbazone tautomers: (a) thione ,(b) thiol

The ability of these forms to chelate delicate substances in solution in an equilibrium state is critical [90, 91] Concerning their biological properties, including antitumor effects, TSC has been the subject of extensive study [92, 93]. Donor sites on these compounds enable the formation of an extensive variety of metal complexes [94, 95]. Thiosemicarbazone complexes with metals have been observed to possess anti-properties, possibly via mechanisms that target multiple targets [96, 97].

1.4 Previous studies of some thiosemicarbazide and semicarbazide complexes

In 2016 T.A. Yousef et al, prepared Complexes [Mn (HPAPT)Cl] From the reaction of ligand H_2PAPT (1-(2-oxo-2-(phenylamino)acetyl)-4-phenyl this semicarbazide with manganese(II) chloride as in Fig (1-4).

Antibacterial and antitumor properties were observed in its biological activities upon investigation. The complex exhibited reduced biological activity in comparison to the ligand [98].

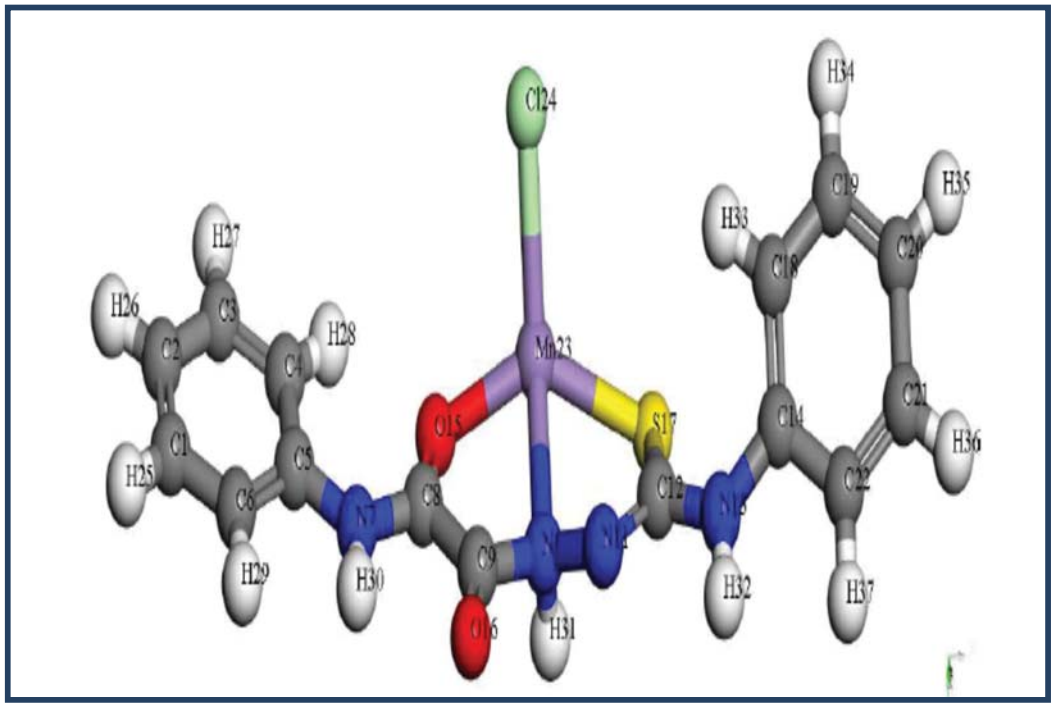


Figure (1-4) Structure Complexes of [Mn(HPAPT)Cl].

In 2019 Muhammad Hamid Khan et al, It was proposed that this complex could be developed as a potential multi-target anticancer candidate after he successfully edited the site N-4 for a series of 2-Acetyl-3-ethylpyrazine thiosemicarbazide to create the compound, which is used as both an antidote

and a medicine to reduce the proliferation of human bladder cancer See figure(1-5) [99].

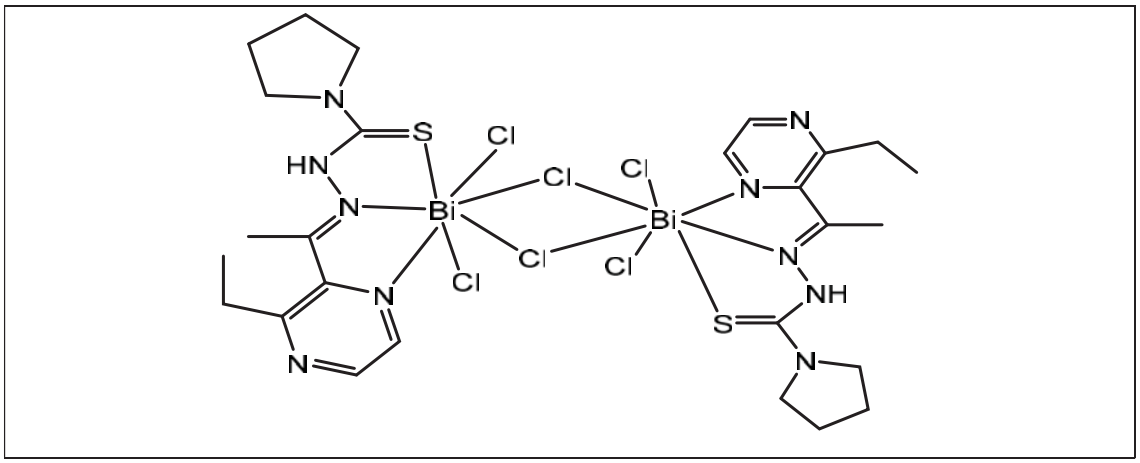
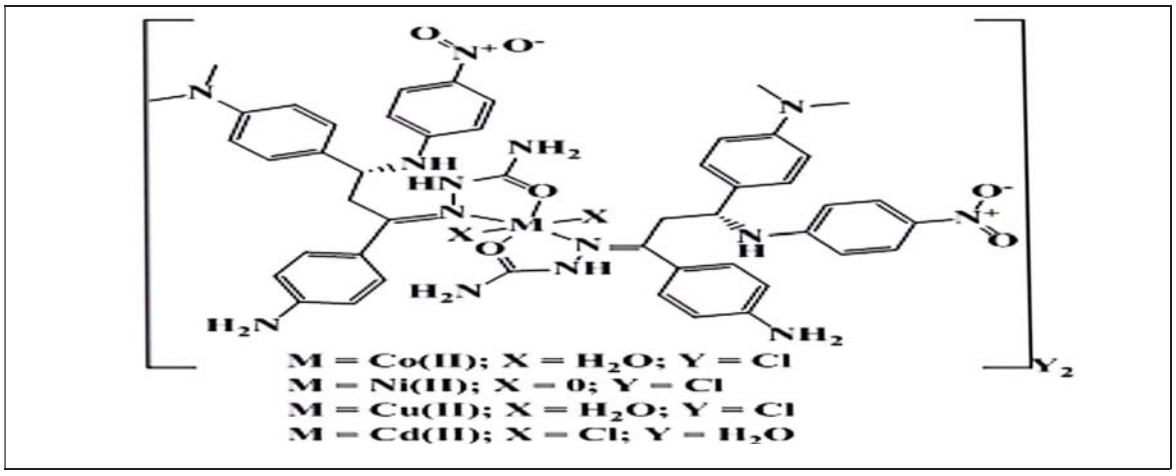


Figure (1-5) Structural of Bi (III) complex

In 2021 Hind A. Saleh *et al*, preparedthe complexes $[Co(L^2)2(H_2O)_2]Cl2$ $[Cu(L^2)2_(H_2O)_2]Cl_2$ 3. $[Ni(L^2)_2]Cl$ 4. $[Cd(L^2)_2Cl2]\ 2H_2O$ by the reaction of the ligand2-(1-(4-aminophenyl)-3-(4-(dimethylamino)phenyl)-3-((4-nitrophenyl)amino)propylidene) hydrazine-1-carboxamide with the (II), Cu(II) and Cd(II) salts, The prepared compounds were tested against G-positive and G-negative bacterial strains and two fungi. The collected data indicated complexes became more effective, compared with the free ligand See Figure (1-6) [100]



Figure(1-6): Synthesis route of semicarbazone Mannich-base ligand.

In 2022 Hala Adnan Dawood *et al* prepared the complexes of the type ;[$LNiCl_2(H_2O)$], [$LCoCl_2(H_2O)$], and [$LCuCl_2(H_2O)$] from ligand N^1-(dimethyl carbamoyl)-N^2-ethylhydrazine-1,2-bis (carbo-thioamide) Various physicochemical methods demonstrated the ligand and its metal complexes to be in their predicted structural form. The following are examples of such analyses: Fourier transform infrared spectroscopy (FT-IR), electronic spectra, nuclear magnetic resonance spectra (^1H and ^{13}C), chloride and metal contents, melting point, molar conductivity, and magnetic susceptibility tests. see Figure (1-7) [101].

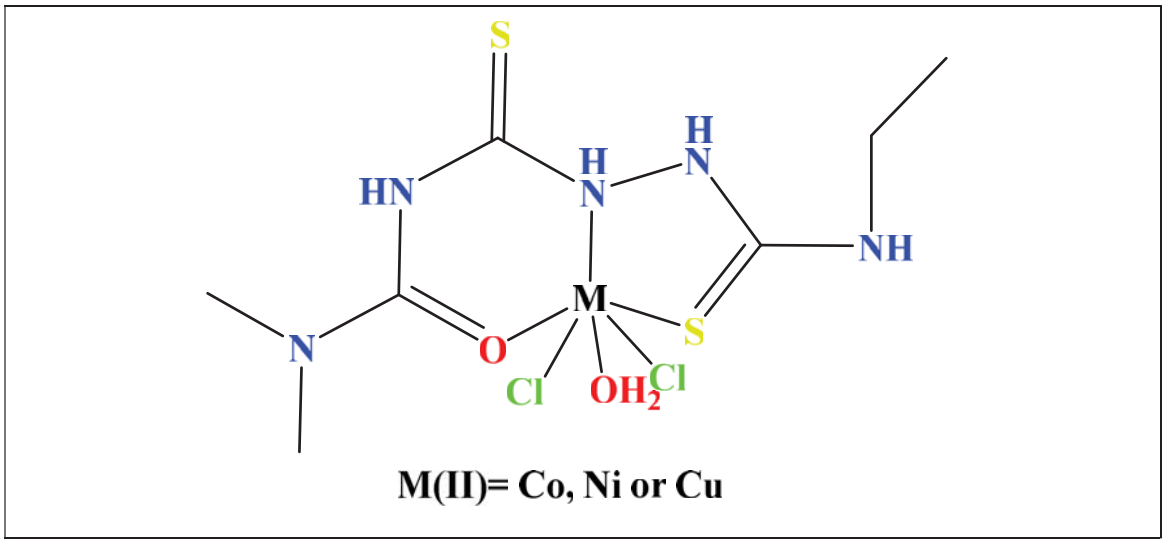


Figure (1-7): Complexes of Co, Ni or Cu

In 2022 Jalan Hameed Sanaa *et al*, prepared the complexes ;[$LNiCl_2H_2O$], [$LCoCl_2H_2O$], and [$LCuCl_2H_2O$] from ligand N^1-(dimetheylcabomoyl)-hydrazine-1,2-bis (carbo-thioamide) The entity of the expected structure of the ligand and its metal complexes were illustrated through a range of physicochemical techniques. These include; FT-IR, electronic spectra, ^1H- and ^{13}C- NMR spectra, elemental analysis (CHNS), chloride content, metal content, melting point, molar conductivity, and magnetic susceptibility measurements see Figure (1-8) [102].

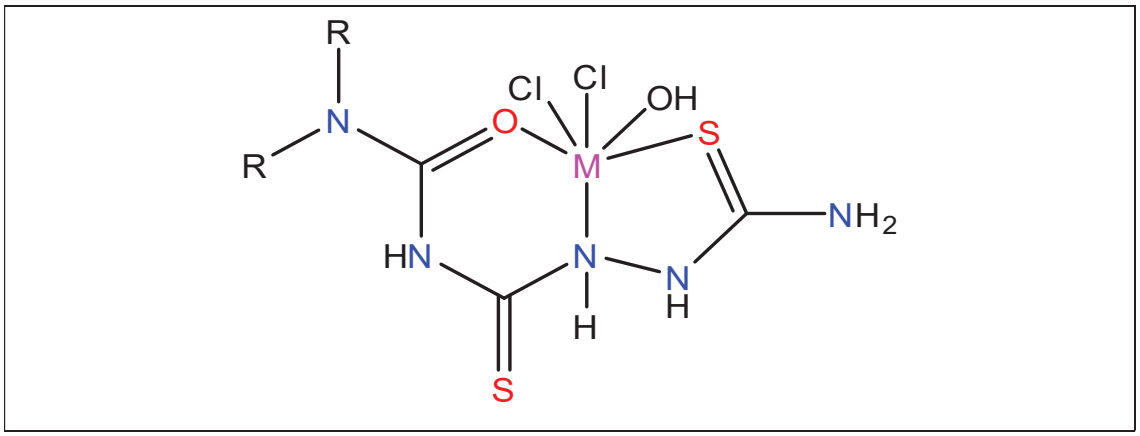


Figure (1-8): complexes of Co, Ni or Cu

In 2022 Laith Shadhin Tamer *et al*, prepared the complexes ;[$LNiCl_2H_2O$], [$LCoCl_2$ (H_2O)], and [$LCuCl_2$ (H_2O)] from ligand N^1-(dimethyl carbamoyl)-N^2-methylhydrazine-1-2- bis(carbo-thioamide). the entity of the expected structure of the ligand and its metal complexes were illustrated through a range of physicochemical techniques. These include; FT-IR, electronic spectra, ^{1}H- and ^{13}C- NMR spectra, elemental analysis (CHNS), chloride content, metal content, melting point, molar conductivity, and magnetic susceptibility measurements see Figure (1-9) [103].

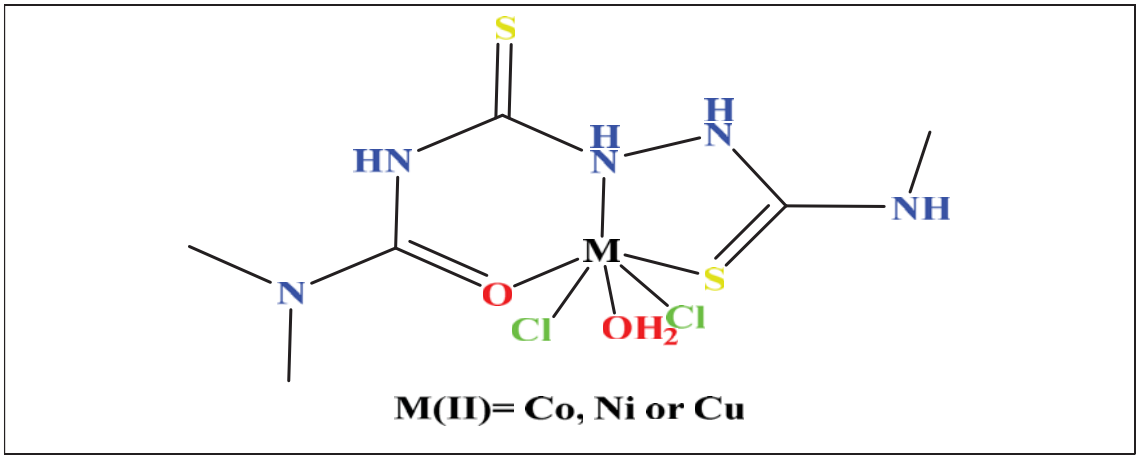
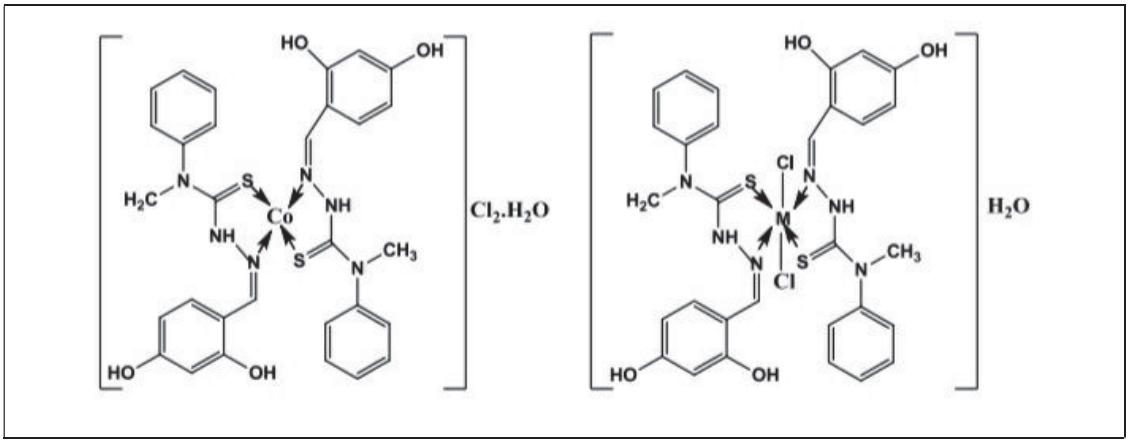


Figure (1-9): complexes of Co, Ni or Cu

In 2023 Abul Monsur Showkot Hossain. ***et al***, prepared Complexes Ni^{+2} Cu^{+2} , and Co^{+2} with 2,4-dihydroxy benzal-aldehyde N(4)-methyl (phenyl)thiosemicarbazone see figure (1-10) [104].



Figures (1-10) Metal complexes of Ligand.

In 2023 Suryansh Chandra. ***et al*** prepared the complex

Ni $(Hppts)_2].CHCl_3$ (1a), $[Ni(Hppts)_2].(CH_3)_2SO$ (1b) and $[Co(Hppts)_2]$ (2) complexes of 1-picolinoyl-4-phenyl- $[Cu\ (DCTS)_2(H_2O)_2].2H_2O$ $[Co\ (DCTS)_2(H_2O)_2].3H_2O$ From the Ligand 1-picolinoyl-4-phenyl-3-thiosemicarbazide (H_2ppts) The synthesized complexes have been characterized by UV-vis., Infrared, and NMR spectrometry. Furthermore, complexes 1a and 1b were characterized by single-crystal X-ray diffraction data. see figure (1-11) [105].

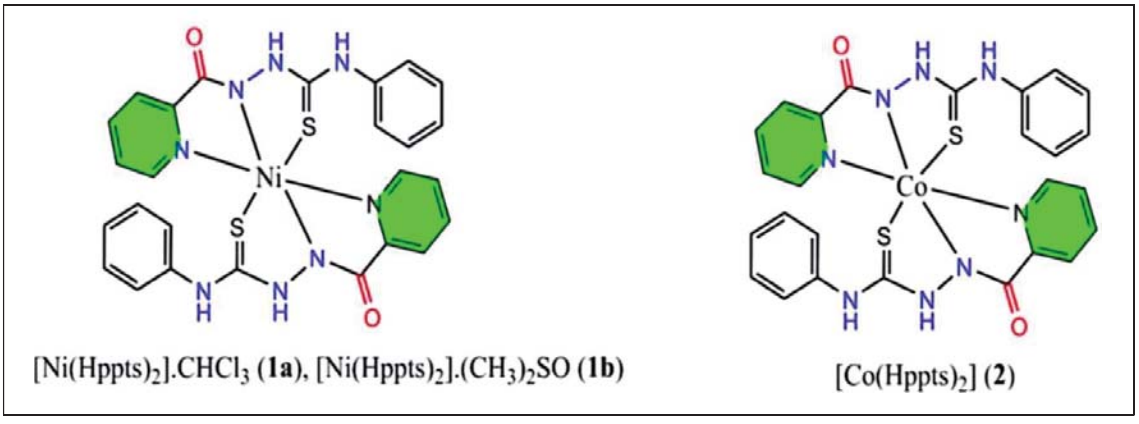


Figure (1-11) Synthesis of the complexes 1a, 1b, and 2.

In 2023 Chérifa Boulechfar *et al* , prepared the complexs Mn(II), Co(II), and Zn(II) with 2-furaldehyde semicarbazone from ligand 2-(furan-2-ylmethylene)hydrazine-1-carboxamide see Figure(1-12) [106].

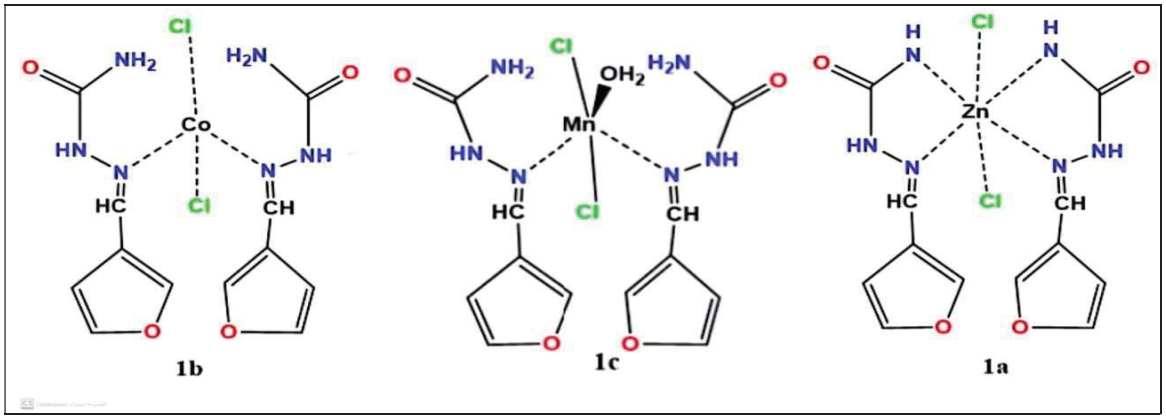


Figure (1-12): Synthesis of transition metal complexes with Schiff base;2-furaldehyde semicarbazone.

In 2024 Ribhu Maity et al studied an in-depth analysis of the biological characteristics of Cu (II) complex ($C_{22}H_{24}Cu_2N_6O_{10}$) obtained from an array-semicarbazone ligand derived (L) from the condensation of 2,4-dihydroxy acetophenone and semicarbazide. The binding behavior of this complex with calf thymus DNA (CT-DNA) and bovine serum albumin albumin (BSA) protein was explored using a combination of experimental and theoretical approaches see Figure (1-13) [107].

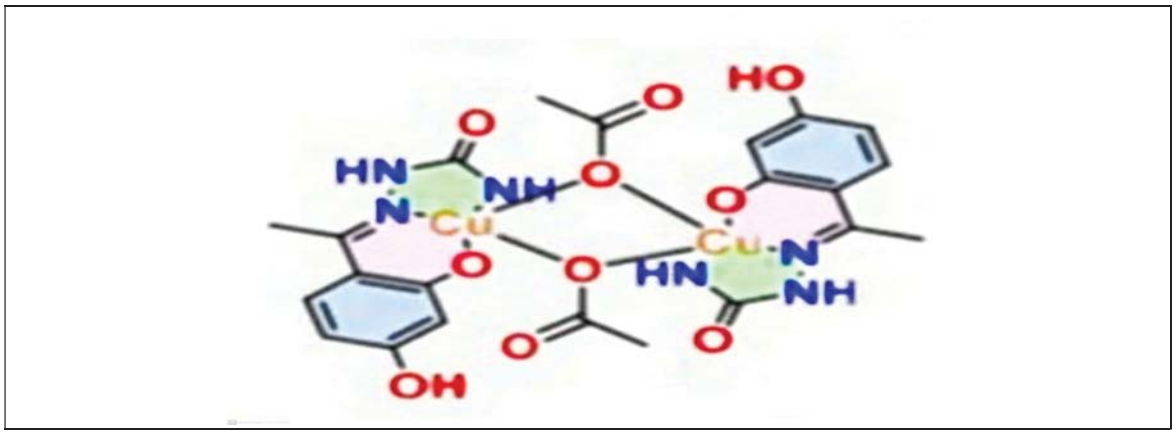


Figure (1.13) the synthesis of ligand and its copper (II) complex.

1.5 Semicarbazide and Thiosemicarbazide Transition Elements.

1.5.1 Manganese Complexes

It can exist in mixed valence states or any of the five oxidation states; it is essential for normal human and animal function; and it serves as an active site for metalloproteins [108] It sets up a tetranuclear manganese complex within photosystem II . [109]. The enhanced efficiency of manganese coordination compounds as homogeneous catalysts in oxidation reactions is being observed. Furthermore, manganese is of paramount importance in a multitude of enzymatic systems, such as dioxygenase, dismutase, peroxidase, and dismutase, in which mononuclear manganese active sites are indispensable [110]. Manganese metal complexes are of great importance in the field of bioinorganic chemistry [111]. They exhibit noteworthy biological activity when they engage in reactions with ligands that donate nitrogen and oxygen, such as thiosemicarbazone and semicarbazone, across a range of oxidation states [112].

In 2023 Anita, Priyanka et al, prepared complex Co(II) and Mn(II) with ligand (Z)-2-(2-methyl-1-phenylpropylidene)hydrazine-1-carbothioamide Ligand and its metal complexes were analyzed through Fourier Transform Infrared (FTIR), Proton Nuclear Magnetic Resonance (^{1}HNMR), Carbon 13 Nuclear Magnetic Resonance (^{13}CNMR), Mass, and X-ray Diffraction (XRD). The anticancer activity has been performed against human liver hepatoma (Hop-62), breast (MCF-7), cervix (HeLa), colon (HT-29), and leukemia (K562) cell lines. The outcomes revealed that the metal complexes revealed good antimicrobial, antituberculosis, and anticancer. see figure (1-14) [112].

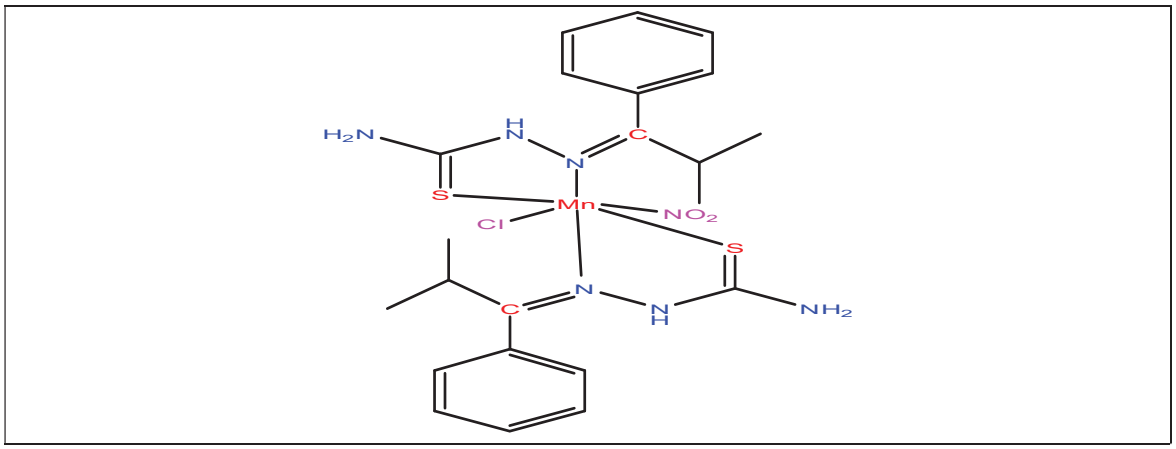


Figure (1.14) The synthetic metal complexes

In 2022 Nesma Salah1 *et al* synthesized the semicarbazide complexes with A novel semicarbazone NOO ligand, H^2L, was synthesized. The ligand reacted with metal ions such as Mn(II) in a molar ratio of 1:1 (M:L). The H^2L ligand and its metal complexes were characterized by electronic, infrared, mass, nuclear magnetic resonance, electron spin resonance spectra, as well as elemental analysis, thermal analysis, and molar conductance see Figure (1-15) [113].

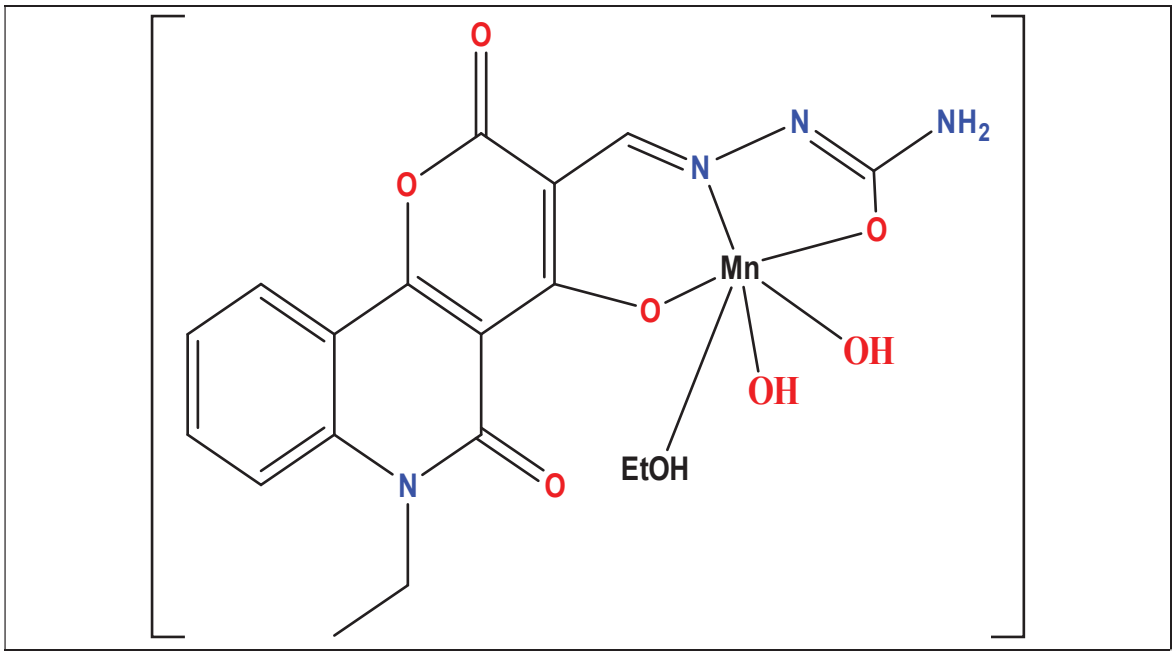


Figure (1-15): Complex of Mn (II)

1.5.2 Cobalt Complexes

Cobalt complexes have managed to garner attention from researchers as potential anti-cancer agents due mainly to their active participation in the synthesis of vitamin B12, a crucial regulator of DNA synthesis. [114].

In 2020 A.A.M. Belal et al, synthesized thiosemicarbazide complexes Co^{+2} by condensation of 2-hydroxybenzaldehyde with substituted thiosemicarbazide see figure (1-16). The electronic spectral data is in favor of an octahedral geometry of the Cu^{+2}, Ni^{+2}, and Co^{+2} complexes but Zn^{+2} is in four coordinated geometry.

The ligand and its Cu^{+2}, Co^{+2}, Ni^{+2}, and Zn^{+2} complexes were tested for antimicrobial activity against some pathogens which gave good efficacy [115].

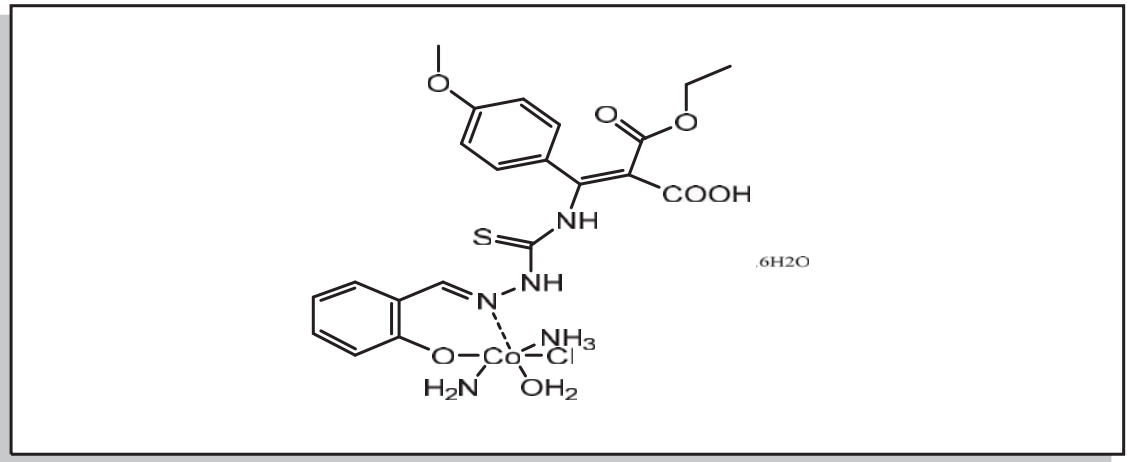


Figure (1-16) Complexe of Co(II)

In 2022 Suher M. Dawoud *et al*, prepared Complex Cobalt with 2-(2-hydroxy-3-methoxybenzylidene)hydrazine-1-carboxamide were synthesized. The ligand was structurally characterized by FTIR, ^{1}HNMR, and ^{13}CNMR spectroscopy. The interaction activity of ligands and complexes was investigated with DNA by spectroscopical and physical methods see Figure(1-17) [116].

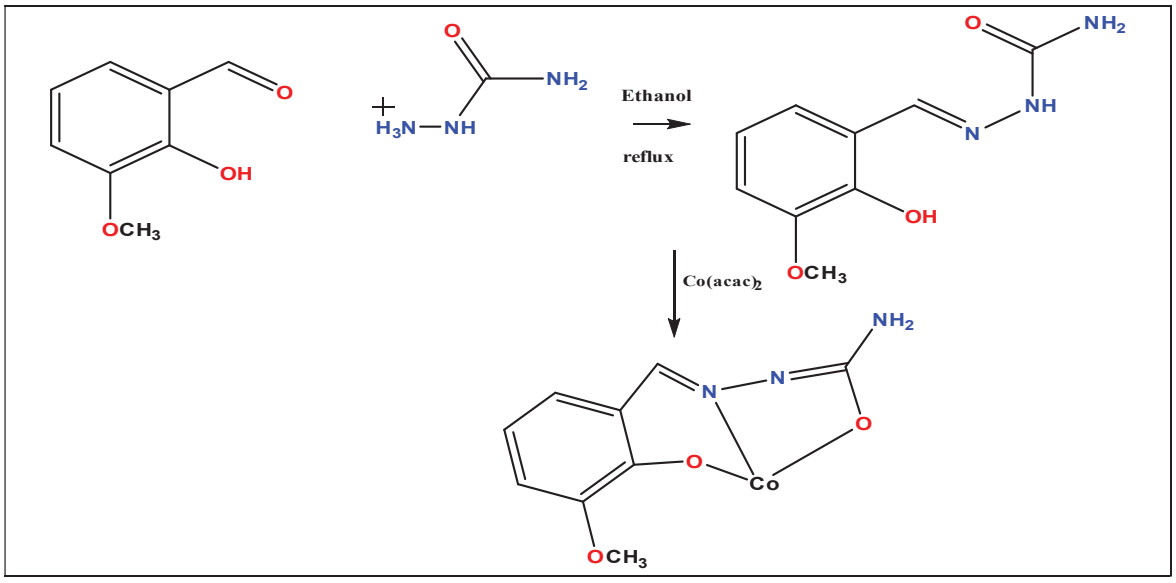


Figure (1-17): Ligand and complex general synthetic procedure

1.5.3 Nickel Complexes

Nickel is an indispensable element in the biosynthesis of hydrogenases and ureases, both of which are critical for the formation of DNA. DNA, serving as the principal target of therapeutic interventions, transports genetic information and is indispensable for cellular division and the proliferation of diverse malignancies. [117] Biologic activity against the bacterium test has been observed in six coordinated Ni^{+2} complexes with thiosemicarbazone and semicarbazone ligands [118]. whereas antibacterial properties have been observed in labile four coordinated Ni^{+2} complexes with tridentate thiosemicarbazone and semicarbazone ligands. The major therapeutic target is DNA, which is made up of fundamental enzymes like ureases and hydrogenases. DNA is important for cell division and the development of many malignancies [117].

In 2017 Hanane Zine et al, prepared a nickel complex from the 2,5-bis(pyridine-2-yl)-1,3,4thiadiazole ligand as shown in Figure (1-18), which proved its efficacy as an anti-fungal [119].

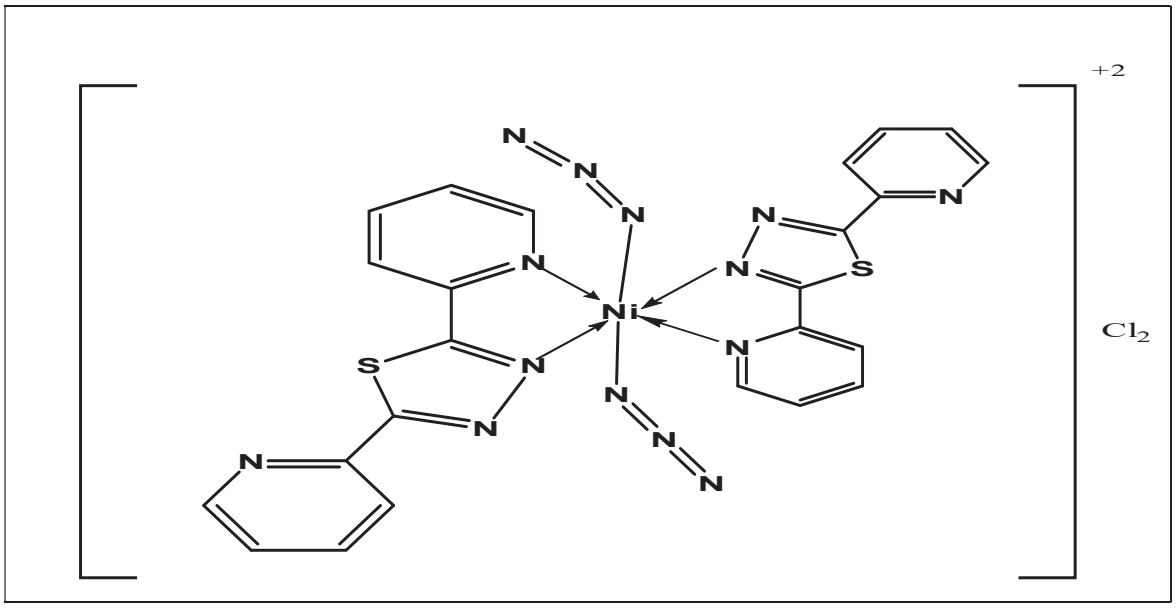
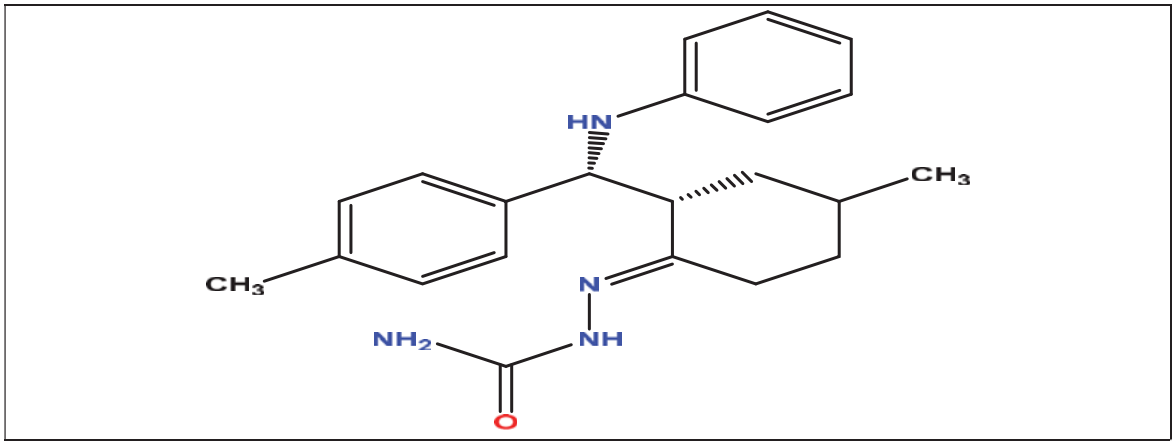
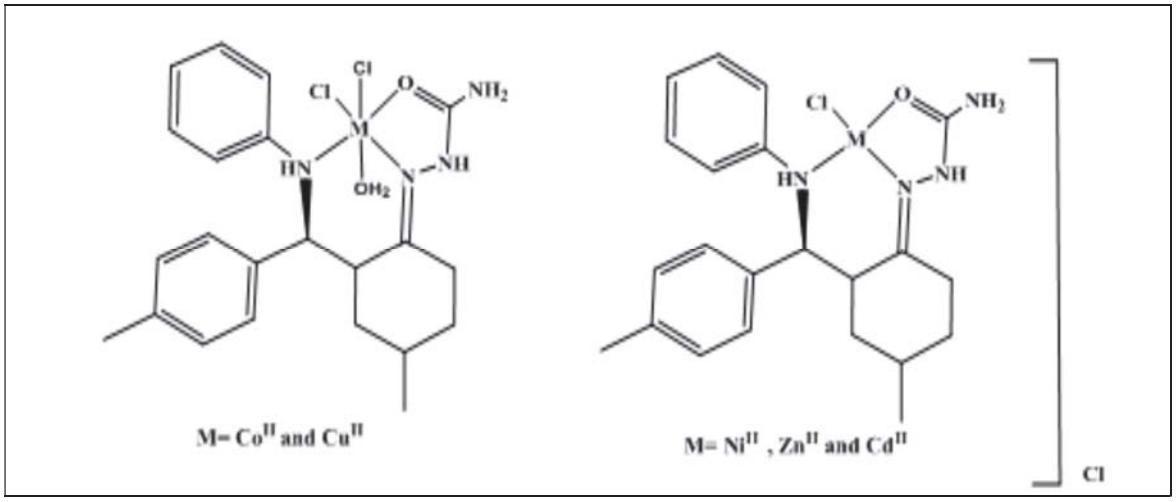


Figure (1-18) The nickel complex of the ligand 2,5-bis(pyridine-2-yl)-1,3,4thiadiazole

In 2020 Samraa Ali Hussein *and Enaam Ismail Yousif* synthesized the semicarbazide complex Ni^{+2} by ligand ((2-((2S)-4-methyl-2-((R)(phenylamino)(prolyl)methyl) cyclohexylidene) hydrazine-1-carboxamide) (HL) The reaction of the ligand with Ni^{+2} ion in a (1:1) (L: M) mole ratio gave the title complexes. To characterize the ligands and complexes, physicochemical methods were used as needed. Among these are the following: FT-IR and electronic spectra; elemental microanalysis; magnetic susceptibility and conductance; and 1H and ^{13}C-NMR and mass spectra. see Figure (1-19) and (1-20) [120].



Figure(1-19):Chemical structure of semicarbazone ligand (HL)



Figure(1-20): Synthesis route of HL complex Ni.

1.5.4 Copper Complexes

Copper is considered essential due to its critical role in a multitude of mineral enzymes. In recent times, there has been an increased acknowledgment of its potential as a non-platinum metallic cancer drug, owing to its broad therapeutic spectrum and diminished adverse effects in cancer biology. Its anti-cancer properties are characterized by tumor inhibition. [121] An essential component of all living things, copper is involved in various metabolic processes, including mitochondria respiration, iron absorption, and redox reactions catalyzed by enzymes [122]. Semicarbazones and thiosemicarbazones do not have any coordination and have lower biological activity than Cu^{+2} and Fe^{+2} metal complexes. Complexes involving bis(thiosemicarbazone) and bis(semicarbazone) ligands and copper (II): structural varieties Condensing 4,6-diacetyl resorcinol with thiosemicarbazide and semicarbazide, respectively, produced the two symmetrical bis(carbazone) ligands H_4L^1 and H_4L^2.

In 2013 Saad .K.Dawood and Falah.M.Fakhree , prepared the complexes with A new ligand 2-(5-hydroxy pentanol) hydrazine carboxamide prepared from the reaction of pyridine-2,6-dicarboxylic acid and glutaric acid with semicarbazide by microwave irradiation in the solid state, then was reacted with some transition metal(II) ions M = Cu (II) see Figure (1-21) [123]**.**

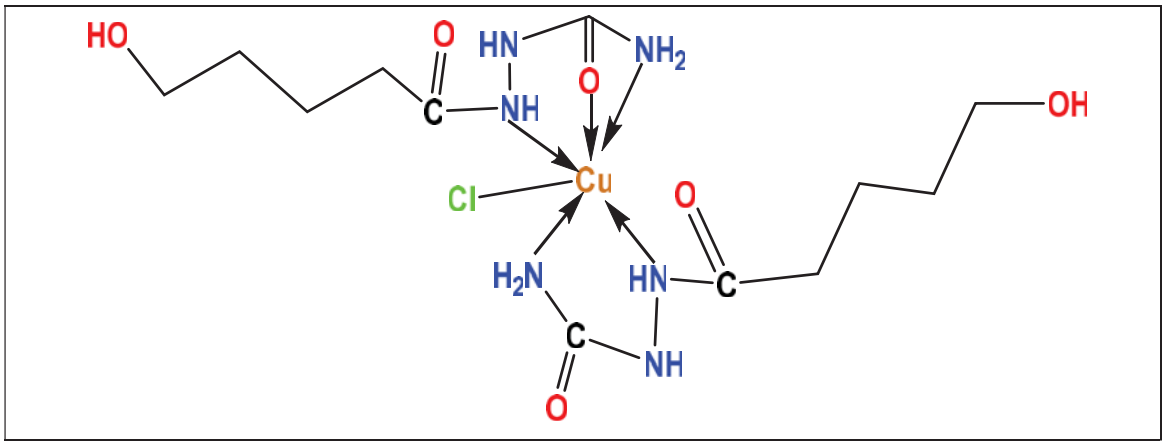


Figure (1-21): Proposed structure of the complex Cu

In 2022 Tarek A. Fayed et al synthesized Thiosemicarbazide copper (II) complexes $[Cu_2(HL^1)2(H_2O)2Cl_2].H_2O$ (1) and $C_{24}H_{26}C_{l2}Cu_2N_{10}O_5S_2$ $[Cu_2(HL^2)2(H_2O)2Cl_2].2H_2O$ (2) $C_{22}H_{30}C_{l2}Cu_2N_{14}O_6S_4$]

(where H2L1 = 2-picolinoyl-N-(pyridine-2-yl) hydrazine-1-carbothioamide and $H2L^2$ = 2-(2-(2-aminothiazol-4-yl)acetyl)-N- (pyridine-2-yl)hydrazine-1-

CuL^2 -complex had the highest activity of quenching phenazine methosulphate radicals.

Their particular coordination may account for their exceptional antioxidant capacity. These compounds constitute a substantial class of potentially effective antioxidants See Figure (1-22) [124].

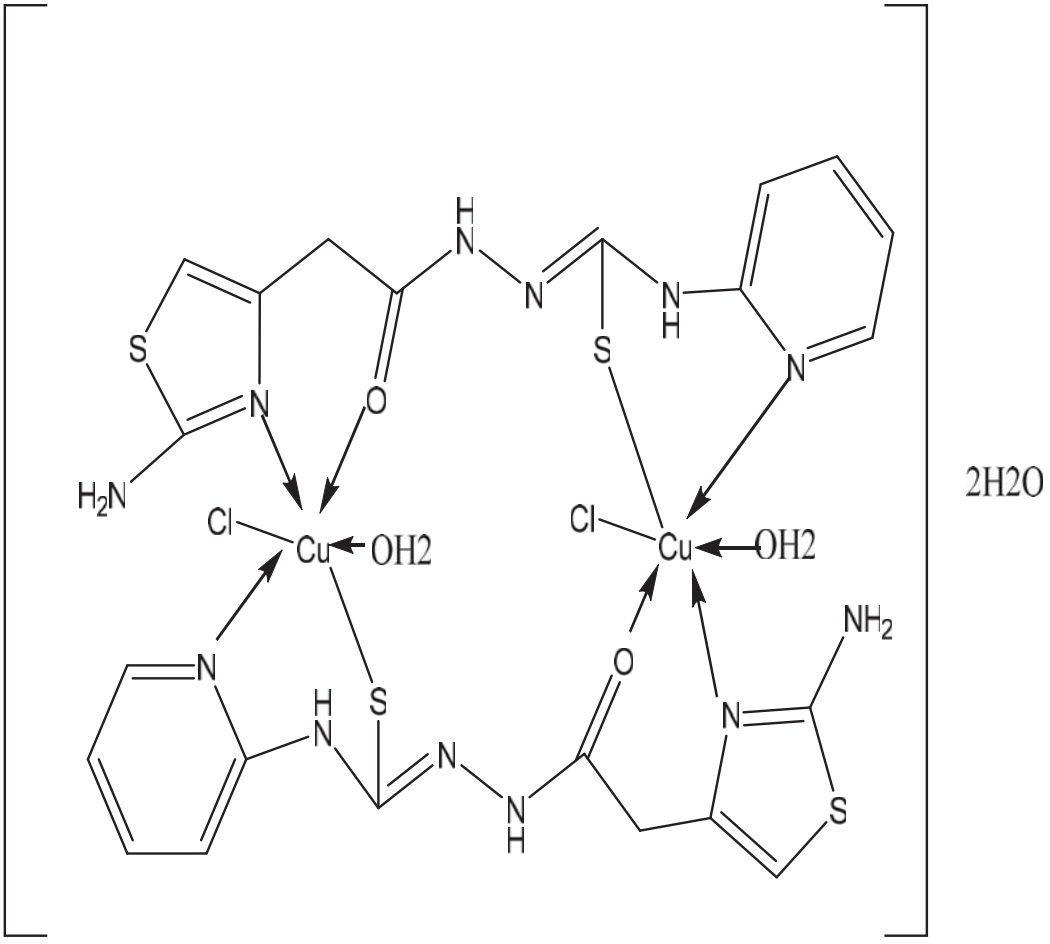


Figure (1-22) Structure of $[Cu_2(HL^1)_2(H_2O)_2Cl_2].2H_2O$

1.6 Aims of the study

Thiosemcarbazide and semicarbazide complexes have been the focus of many researches. Their fabrication and design attract the attention of workers due to their potential applications in many fields such as analytical chemistry, industry, catalysis, and biology. Therefore, the preparation of their compounds requires fall characterization of the chemical structure of the species. The aim of this work could be summarised as follows:

1- Synthesis of two ligands (L^1 and L^2) thiosemicarbazide and semicarbazide derivative.

2- Synthesis of complexes by reaction of one mole of prepared ligands with Mn^{+2} , Co^{+2}, Ni^{+2}, and Cu^{+2}

3- Physicochemical characterization is carried out as necessary to verify the compounds' entities. Such as magnetic moments, conductance, FT-IR, mass spectra, ^{1}H-NMR, ^{13}C-NMR, UV-Vis, spectroscopy microanalysis, and (m.p C^o)

4- Study the bacterial activity of the prepared ligands and their complexes toward gram-positive and gram-negative bacteria