Original Article

# Review Of Semicarbazone, Thiosemicarbazone, And Their Transition Metal Complexes, And Their Biological Activities

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## Abstract

Semicarbazides and thiosemicarbazide condense to form the chemicals semicarbazones and thiosemicarbazones. Using the appropriate aldehydes or ketones with thiosemicarbazide. They are effective synthesis-related intermediates for they are widely employed in the field of medicinal chemistry since they are both pharmaceutical and bioactive compounds. One of the most important goals in medicinal and bioinorganic chemistry is the creation of novel, advantageous bioactive molecules with a variety of biological functions. Antibacterial, antifungal, antioxidant, antiviral, radical scavenger, antitubercular, anticancer, and other properties of semicarbazones, thiosemicarbazones, and their derivatives have been studied. Therapies against cancer, particularly when bound to transition metals. Their capacity to combine with metals to create chelates is thought to be related to their biological actions. The compound's IR and 1H-NMR data have been used to characterize their structures. Studies have been done on substances with the formulae -N=N-, -N-C=S, and the pharmacophore is -CH=N-. To organize the various biological activities of some synthesized semicarbazone and thiosemicarbazone derivatives with transition metals, the synthetic root of some of these derivatives and complexes are reviewed as for biological activities in accordance with this biological potential.

**Keywords:** Semicarbazone, Thiosemicarbazones, Metal Complexes, Antibacterial, Antifungal and Anticancer Therapeutics.

## INTRODUCTION:

Semicarbazide condensation and the reaction of various ketones or aldehydes yield important compounds like semicarbazones and thiosemicarbazones. The semicarbazone derivative known as thiosemicarbazone is created when the oxygen atom in the compound is replaced with a sulphur atom. When these thiosemicarbazones and metallic cations interact, chelating ligands and complexes are produced. Many studies, including those on their antibacterial, antiviral, antibacterial, anti-fungal, and anti-malarial properties, have demonstrated the effectiveness of these complexes. For their pharmacological characteristics, complexes of semicarbzones and thiosemicarbazone ligands and transition metal synthesis are significant[1]. The discovery of chemotherapeutically useful platinum complexes and thiosemicarbazide derivatives. Thiosemicarbazone was used in the chemical's synthesis, and the majority of the compound displayed biological activity[2]. Metallic complexes are typically created by the coordination of transition metals with semicarbazone and thiosemicarbazone ligands, which are typically coupled by their oxygen, nitrogen, and sulphur atoms and take the form of (N,S) bidentate forms or (N,N,S or O,N,S) tridentate forms [3,4]. The antifungal studies of the bidentate ligands with the metal ions Ni (II), Pd (II), and Pt (II) were reported in the spectral synthesis further. Due to their capacity to bind to cell metals[6] and perform antibacterial, antifungal, antimalarial, and antiviral effects, semicarbazones and thiosemicarbazones are of tremendous interest in the domains of chemistry and biology. They primarily serve as chelating ligands with donor imine groups that interact with transition metal complexes to produce unoccupied d-orbitals. The complexes could show bioactivities that the free ligands did not[7]. Semicarbazones and thiosemicarbazones typically serve as ligands, and complexes are created when metallic cations interact. Semicarbazones are important ligands for thiosemicarbazones due to their pharmacological properties and their application in the creation of transition metal complexes. After the Thiosemicarbazide derivatives, notably thiosemicarbazones, were discovered, platinum compounds with chemotherapeutic potential compounds with biological activity that have been created. Thiosemicarbazones and semicarbazones ligands. Transition metal's typical donor atoms of oxygen, nitrogen, and sulphur coordinate to these to form metallic complexes. Select the tridentate form (N, S), (N, N, S), or (N, N, S) form. The antifungal studies of the bidentate ligands with the metal ions Ni (II), Pd (II), and Pt (II) were reported in the spectral synthesis further[5]. (II). Because of their capacity to bind to cell metals [6] and perform antibacterial, antifungal, antimalarial, and antiviral effects, semicarbazones and thiosemicarbazones are of tremendous interest in the disciplines of chemistry and biology. The majority of the time, they function as chelating ligands with donor imine groups that interact with transition metal complexes to create vacant d-orbitals. Bioactivities that the free ligands do not exhibit may be seen in the complexes [7]. By taking into account the biological capabilities of thiosemicarbazones, semicarbazones, and their mixtures. Here, we had observed that the derivatives of transition metal complexes and look at some of their synthetic antecedents. Compounds with antibacterial, antifungal, antimalarial, antineoplastic, and antiviral properties have a wide range of possibilities in pharmaceutical and medicinal chemistry research and development for biological systems.

## BIOLOGICAL SYSTEM'S ROLE FOR COMMON TRANSITION METALS:

Semicarbazone and thiosemicarbazone biological characteristic are frequently correlated with metal ion coordination. Lipophilicity which control the velocity of entrance into the cell is the first modified by coordination[8]. Additionally, coordination could significantly reduce medication resistance[9]. Semicarbazone and thiocarbazone frequently act as chelating ligand and form complexes with metallic cation. They are versatile ligand that can be anionic or neutral. Semicarbazone and thiosemicarbazone ligand are found in the chemistry of some of this often-binding transition metal's, which is a bioactive molecule.

**Nickel: -** The specific hydrogenase and dehydrogenases enzymes can operate as active sites on nickel in biological system. The active participation of nickel centers in the mutagenicity of nickel compounds occurs at the active sites of several ureases, methyl coenzymes-M-methyl reductase, and hydrogenase[10]. While six coordinated Ni (II) complexes with thiosemicarbazone and semicarbazone ligand have biological activity against the bacterium test[11], labile four coordinated Ni (II) complexes with tridentate thiosemicarbazone and semicarbazone ligand exhibit antibacterial properties. Additionally, nickel (II) complexes containing octadiensemicarbazones strongly inhibit staphylococcus aureus and eschericіan coil[12].

Activities of Nickel (II) complexes of thiosemicarbazone and semicarbazone in antineoplastic and cytotoxic reaction: - Thiosemicarbazone nickel (II) complexes were found to be effective cytotoxic agents in rodent and human tissue grown tumor cells. In the several an nor histology types, each drug showed a somewhat distinct profile. The Ehrlich ascites carcinoma exhibited the strongest in vivo activity when exposed to the nickel complex. This substance specifically inhibited the activities of DNA polymerase, PRPP-amido transferase, IMP-dehydrogenase, dihydrofolate reductase, TMP-kinase, and thymidylate synthetase as well as the L1210 DNA and purine syntheses. After a 24-hour incubation, L1210 DNA strand scission was visible, and DNA viscosity was decreased. There was no L1210 DNA topoisomerase II inhibitor in the nickel complexes.

**Zinc: -** is a vital trace element that is found in large amounts in human red blood cells[13]. Those are the second-most prevalent trace element in humans, with an average adult body weight of 2.3 g. Zinc (II), a symmetrical (d10) borderline metal, interacts strongly with O, N, and S donor ligands. Zinc is an essential cofactor for the acknowledged biological functions (most associated with protein and enzymes). It can be essential for maintaining the stability and structure of proteins in the human body or directly participate in chemical catalysis (zinc enzyme)[14]. Each of the six classes of enzymes, as well as the more than 300 catalytic, co-catalytic, and Structural site) [15]:

Transferases – isomerases

Oxidoreductases – lyases

Hydrolyses – ligases

Bidentate ligands' thiosemicarbazide and thiosemicarbazone complexes with tetrahedral and octahedral Zn (II) structures were reported[16]. The carbonyl group functions as the third coordinating center in zinc complexes, which are also supplied by ligands such as ethylacetoacetatesemicarbazone and thiosemicarbazone.

**Cadmium: -** Because of this, cadmium-containing ores are only occasionally discovered[17]. Cadmium forms complexes by chelating with nitrogen donor ligands such as semicarbazone and thiosemicarbazone compounds[18]. The most stable Cd (II) complexes are those formed by soft donor atoms (S>>N > O). The stability of the complexes improves along with the amount of coordination groups provided by the semicarbazone and thiosemicarbazone derivative ligands[19].

**Copper: -** Copper, a first-row transition element essential for life[20], is present in the majority of living organisms. Copper is used in biological systems to catalyze redox reactions, most notably the reduction of oxygen to water[21]. Because there are unpaired electrons present, the copper (II) complexes are all paramagnetic. Biological activity[22] has led to a rise in chemical and biological studies on Schiff base compounds with thiosemicarbazone and similar transition metal complexes. The biological activity of Cu (II) and iron (II) metal complexes is higher than that of semicarbazones and thiosemicarbazones, which lack coordination.

Structure variety in bis(thiosemicarbazone) and bis(semicarbazone) ligand copper (II) complexes: In order to create the two symmetrical bis(carbazone) ligands $H_4L_1$ and $H_4L_2$, 4,6-diacetylresorcinol was condensed with thiosemicarbazide and semicarbazide, respectively. By performing elemental tests, IR, electronic, and 1H NMR spectroscopy, their structures were clarified. Both ligands have two pairs of SNO ($H_4L_1$) or ONO ($H_4L_2$) coordinating sites and are tetrabasic. We generated dimeric, binuclear, and trinuclear Cu II complexes as well as adducts with organic bases. $H_4L_1$ reactions with a variety of Cu II salts, such as Cl, AcO, $SO_4^{2-}$, $NO_3$, and $ClO_4$, in addition to Cu I as Cu I, produced various binuclear complexes depending on the salt and the conditions of the reaction, with the exception of $CuCl_2$, which produced a trinuclear complex with a distinctive mode of bonding.

**Cobalt: -** The most common kind of ligand used to stabilize the cobalt (III) ion in aqueous solution is the chelating N, O donor ligand. These cobalt (III) complexes generated from ligand donor sets have been employed as antibacterial or antiviral medications. One of the most promising classes of Co (III) complexes integrating N, O donor ligands is the Cobalt (III) complexes series[23]. Dioxygen carriers, oxygen activators[24], and enantioselective reduction are also utilized. Furthermore, it joins forces with semicarbazone to produce bioactive compounds[25].

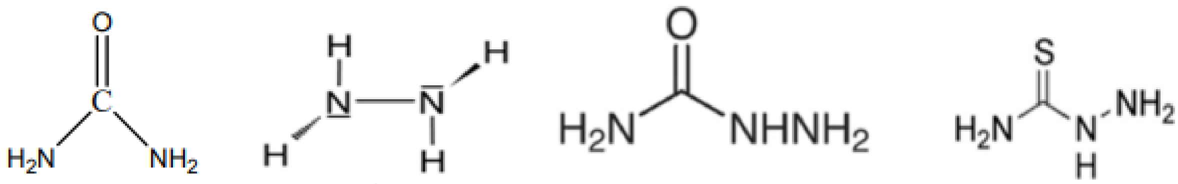
**Manganese: -** is essential for appropriate physiological function in both humans and animals. Metalloproteinase can engage in activity there. In metalloproteinase, it can occur in mixed valence states[26] or any one of the five oxidation states. Photosystem II contains the astra nuclear manganese complex [27]. Manganese coordination compounds are increasingly efficient as homogenous catalysts in oxidation processes. Mononuclear manganese active sites have been found in a number of enzymatic systems, including peroxidase, peroxide dismutase, and dioxygenase[28]. Complexes of manganese metal are important in bioinorganic chemistry[29]. The chemistry of manganese is currently undergoing intense biological activity in a variety of nitrogen and oxygen donor ligand combinations, including semicarbazone and thiosemicarbazone[30].

## SEMICARBAZONE AND THIOSEMICARBAZONE CHEMICAL BONDING TO TRANSITION METAL'S: -

The production of semicarbazone and thiosemicarbazone begins with a molecule called semicarbazide. Generated when urea is treated with hydrazine as:

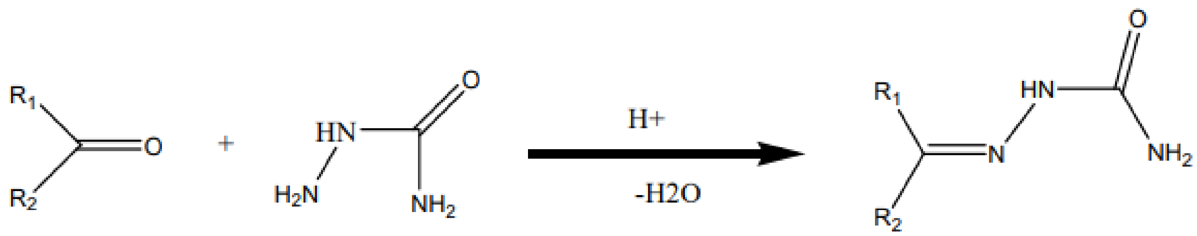
$OC(NH_2)_2 + N_2H_4 \rightarrow OC(NH_2)\ (N_2H_3) + NH_3$

**Structures:**



Urea Hydrazine Semicarbazides Thiosemicarbazide

Condensation processes result in aldehyde or ketone derivatives such semicarbazones and thiosemicarbazone. Between a ketone or an aldehyde and a semicarbazide or thiosemicarbazide. As shown in scheme bellow.




**Scheme-1: -** synthesis of Semicarbazone

A review of semicarbazone and thiosemicarbazone found that the C=N-NH-CO-$NH_2$ backbone of free unsubstituted semicarbazones in the solid state is generally planar, with O atom trans to azomethine N atom[31].

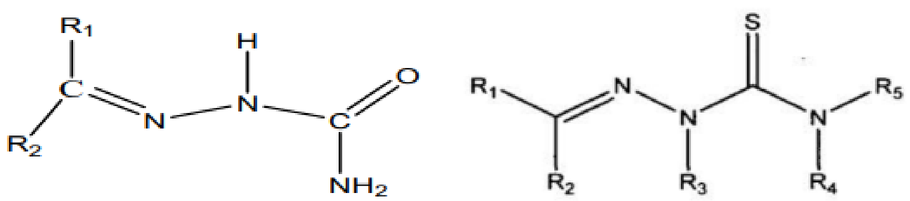


**Figure- 1: -** General Structure of semicarbazone & Thiosemicarbazones

**Schiff Base: -** Hugo Schiff gave the term "Schiff base" to molecules having functional groups that contain carbon-nitrogen double bonds in which the nitrogen atom is connected to an aryl or an alkyl group rather than to hydrogen[32]. The general equation for Schiff bases is R1R2C=NR3, where R stands for an organic side chain. Azolethine and Schiff base are equivalent in this definition. Some people only consider secondary aldimines to be azomethines with a hydrogen atom connected to the carbon, or RCH=NR'[33] in general.

Due to the nitrogen chain, the Schiff base is an imine that is stable. An aniline-derived Schiff base, where $R_3$ Is a substituted phenyl, also known as an anil, which is a phenyl.

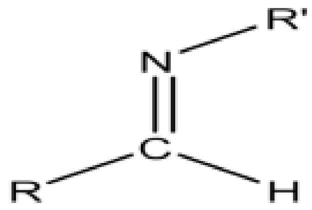


**Figure- 2: -** General Structure of a Schiff Base

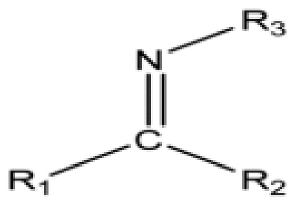


**Figure- 3: -** General Structure of an azomethine

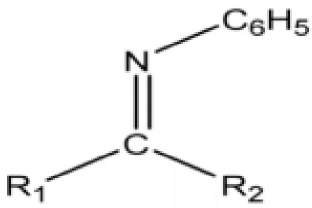


**Figure- 4: -** General Structure of an anil

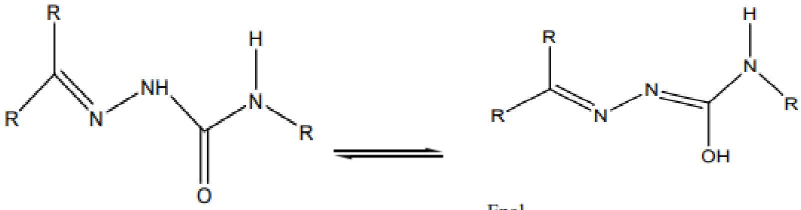
Interesting coordination mechanisms can be seen in the Schiff bases in the form of semicarbazone and thiosemicarbazone. The coordination mode with transition metals is influenced by the quantity and kind of the substituent [34]. As a result

The active donor has many binding sites for ligands, depending on the substituent. Studies [35] have shown that the coordination mode of semicarbazone is highly sensitive to even tiny alterations in the experimental apparatus. They are particularly flexible ligands that can coordinate to metals as neutral molecules or after deprotonation as anionic ligands. They can adopt a variety of different coordination modes.

Thiosemicarbazones and semicarbazones function as ligands as a result of: -

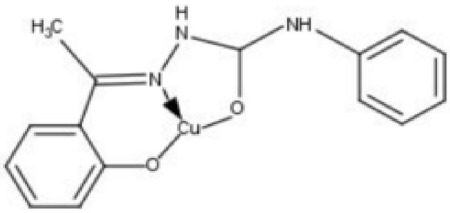
i. They tend to be more coordinated.
ii. They build stronger complexes.
iii. Their selectivity is higher.
iv. They might develop macrocyclic ligands.

They can produce a wide range of innovative and unique compounds with increased biological activity [36]. A Semicarbazones have a special characteristic in that they primarily exist in the solid state in the keto form, but in liquid. The solution state exhibits a keto-enol tautomerism[37]. The enol form can deprotonate, while the keto form serves as a mono-anionic bidentate ligand in metal complexes. Semicarbazones are adaptable ligands in both neutral and anionic forms, as shown in below.



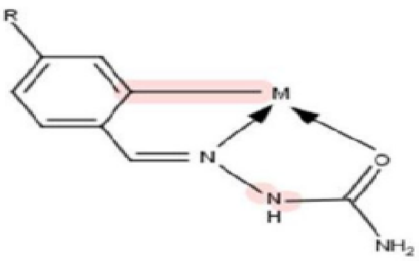

**Scheme- 2: -** keton-enol tautomerism of semicarbazones

In both tautomeric forms, the electrons effectively delocalize along the semicarbazone moiety. An aromatic substituent on the semicarbazone skeleton can further improve the delocalization of electron charge density. When these compounds' semicarbazones react with metallic cations, complexes are created that exhibit chelating behaviour when coordinated to a metal center and enhance delocalization by using metal chelate rings. The opportunities for coordination are further increased if the substituent includes additional donor atoms. For the majority of the complexes, semicarbazone was designed as a tridentate ligand, while it occasionally exhibits as a potential quadridentate when the second pyridyl nitrogen is involved in the coordination process [38].



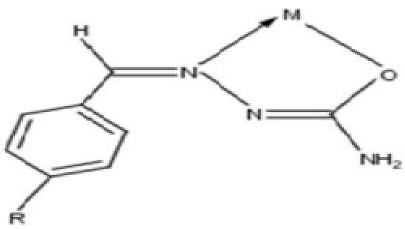
O, N, O-tricoordination

Here are the several ways that substituted benzaldehyde semicarbazone coordinates;

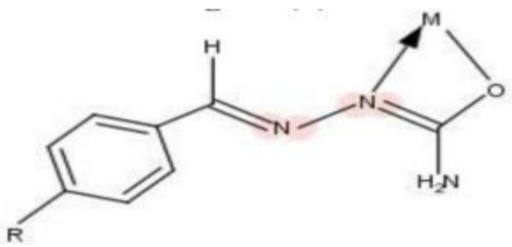


C, N, O-tricoordination

Five-membered chelate formed by N and O coordination.



N, O-donor in an uncommon four-member chelate structure



**Schemes- 3: -**Semicarbazone coordination in several ways or modes

Thiosemicarbazones display thione-thiol tautomerism due to the presence of the NH-C=S group. Strongly they do so in solution as an equilibrium blend of thione and thiol form[39], despite the fact that they do so in thione form[40] ( Framework).

**Scheme- 4: -** Equilibrium mixture of thione and thiol.

There are many different coordination modes that thiosemicarbazone can employ[41]. Most episodes of the series make use of thiosemicarbazone[42]. Sulphur and nitrogen coordinate as bidentate ligands via thione/thiolate[43].

## BIOLOGICAL ACTIVITIES OF SEMICARBAZONE, THIOSEMICARBAZONE AND THEIR METAL COMPLEXES:

Semicarbazones exhibit a diverse range of bioactivities, and both their chemistry and potential pharmaceutical uses have been well studied[44]. Semicarbazones' biological characteristics are frequently correlated with metal ion coordination. First, coordination[45] alters lipophilicity, which regulates the rate of entrance into the cell. Additionally, the free ligand may not be as active as the metal complex[46]. The metal complex may serve as a vehicle for activating the ligand as the cytotoxic agent, or binding to a metal in vivo may be necessary for the mechanism of action. Additionally, coordination could significantly reduce drug resistance. Semicarbazone and thiosemicarbazone typically exhibit chelating ligand behaviour and interact with metallic cations to form complexes. Certain compounds with semicarbazones and thiosemicarbazones have garnered a lot of interest due to their diverse applications as antiviral, antibacterial, and possessing antimicrobial and antifungal properties.

A. **Semicarbazones as Anti-Protozoa Agents: -** The treatment of Chagas disease, a significant issue in Central and South America, has led to the development of a range of 5-nitrofuryl semicarbazone (nitrofurazone) derivatives. Trypanosoma cruzi is a protozoan parasite that causes Chagas disease, also known as American trypanosomiasis, and is spread to people by the blood-sucking insects triatome infest and triatome retroviral. On the nitrofurazone moiety's N-4, a substitute has been added with various electronic and steric properties [47]. The substances were examined in vivo in parasite-infected mice and in vitro against T. cruzi epimastigote [48].

B. **As antibacterial and antifungal activity: -** Wide-ranging antimicrobial action is observed in thiosemicarbazones and their metal complexes[49]. Different 2-acetylpyridine thiosemicarbazones were tested against clinical isolates of bacteria to see how effective they were at inhibiting bacterial growth. Neisseria gonorrhea, Neisseria meningitides, Staphylococcus faecalis, Streptococcus faecalis, and D Enterococcus[50] were all reported to be inhibited by the substances examined. Similar behaviour was displayed by Pt (II) complexes of 2-acetylpiridine thiosemicarbazone, which were toxic to gram-positive but inactive against gram-negative bacteria. The complexes worked against yeast strain [51]. Additionally, a group of 2-(alpha-hydroxyacetyl) pyridine thiosemicarbazones showed strong inhibitory activity against Staphylococcus aureus, N. meningitides, and both penicillin-sensitive and penicillin-resistant N. gonorrhea. Compared to the comparable 2-acetylpyridine thiosemicarbazones [52], these novel compounds seemed to be less harmful to the host. Antibacterial properties of thiosemicarbazones synthesised from 2,6-diacetylpyridine and 4- and 6-coordinate Ni (II) complexes have been demonstrated[53]. It is possible that activity would be correlated with ligand-replacement abilities[54] given that only the labile complexes showed activity against S. aureus and Bacillus subtilis. Xanthomonas sp., E. coli, and S. aureus were tested on fungi (Macrophomina phaseolina, Fusarium oxysporum), and bacteria (Xanthomonas sp., S. aureus), using derivatives of 2-acetylpyridine, 2-furfuraldehyde, 2-acetylnaphtalene, 2-acetylthiophene, and The complexes' enhanced lipophilicity may have had a role in the fact that they were more active than free ligands. Furthermore, the thiosemicarbazone compounds were more energetic than their semicarbazone counterparts.

It was suggested that the toxicants' primary mode of action is the denaturation of cellular proteins. Chelating substances usually act as powerful metalloenzyme inhibitors, enabling the ligands to function by obstructing the metal-dependent enzymes[55]. The ligands were not as potent against the organisms as the metallic derivatives of titanium and zirconium produced from thiosemicarbazones [56]. Aryl thiosemicarbazones showed good activity against Aeromonas hydrophilic and Salmonella typhimurium [57], while two-formyl pyridine thiosemicarbazones and their oxovanadium (IV) complexes demonstrated powerful in vitro antibacterial activities towards E. coli [58]. Also tested for antibacterial and antifungal action were a large number of additional thiosemicarbazones and metal complexes.

C. And other such activity are antitubercular, antiviral, and antifungal.

## SEMICARBAZONE AND THIOSEMICARBAZONE THERMODYNAMIC AND KINETIC STABILITY WITH THEIR TRANSITION METAL COMPLEXES: -

The stepwise formation constants in the equations below (charges deleted for simplicity) [61] are used to denote the thermodynamic stability of metal ions with semicarbazone and thiosemicarbazone.

$$M + L \Leftrightarrow ML \qquad K_1 = \frac{[ML]}{[M][L]}$$

$$ML + L \Leftrightarrow ML_2 \qquad K_2 = \frac{[ML_2]}{[ML][L]}$$

$$ML_2 + L \Leftrightarrow ML_3 \qquad K_3 = \frac{[ML_3]}{[ML_2][L]}$$

Constants of general stability as:

$$M + L \Leftrightarrow ML \qquad \beta_1 = \frac{[ML]}{[M][L]}$$

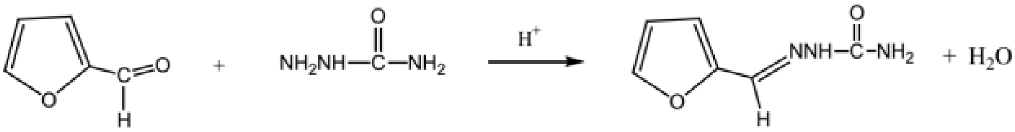
$$M + 2L \Leftrightarrow ML_2 \qquad \beta_2 = \frac{[ML]}{[M][L]^2}$$

$$M + 3L \Leftrightarrow ML_3 \qquad \beta_3 = \frac{[ML]}{[M][L]^3}$$

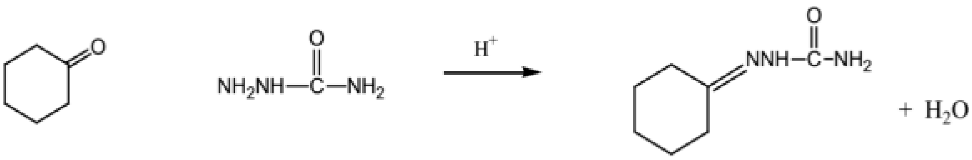
Equation represents the relationship between the stepwise and overall stability constants:

$$B_n = k_1 k_2 \ldots\ldots k_n$$

The formation of metal-ligand complexes in biological systems is influenced by a variety of factors. The study of hard-soft acids and bases is one key component[59]. The concentrations of the metal and ligand at the site of complexation are influenced by local concentration gradients, membrane permeability to metals and ligands, and other factors. Complexation, solubility products, and/or acid-base equilibrium constants, collectively known to as “metal ion speciation,” are three competing equilibria that have an impact on complex formation [60]. Ion size and charge, preferred metal coordination geometry, and ligand chlelation effects all have an impact on metal absorption. In order to more precisely assess biological metal-ligand interactions, a “uptake factor” is defined as KML[M], where [M] is the concentration of metal ion and KML is the stability constant $K_1$.A high degree of selectivity for metal species is necessary to concentrate the relevant ions at the necessary places. The ligands that the concerned cation prefers are those that differentiate molecules. The more stable product is the only one that can be controlled by thermodynamics. The substance is made by lowering the activation energy[61].



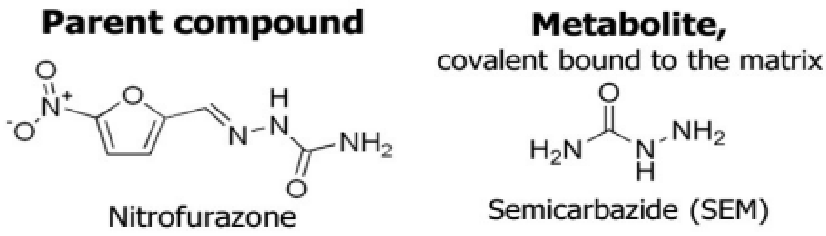

2-furaldehyde (F) semicarbazide (S) 2-furaldehyde semicarbazone (FS)




cyclohexanone C semicarbazide (S) cyclohexanone semicarbazone (CS)

## SEMICARBAZONE AND THIOSEMICARBAZONE'S TOXIC EFFECTS: -

Semicarbazide, a byproduct of the nitrofurane Nitrofurazone (5-nitro-2-furaldehyde semicarbazone), is used as a marker to detect nitrofurane use in livestock.



In order to unify the detection of semicarbazide, a Minimum Required Performance Limit (MRPL) of 1 g/kg is imposed within the EU (Commission Decision 2003/181). Nitrofurane are not allowed to be used in the EU for animal breeding due to their carcinogenic qualities (Commission Regulation 37/2010).

## CONCLUSION: -

An detailed literature review relating semicarbazone, thiosemicarbazone, and related transition metal complexes has been covered in this review. They are possible polydentate ligands due to the presence of amide, imine, and thione groups. The uncoordinated semicarbazone and thiosemicarbazone are much less physiologically active than the transition metal complexes. Numerous writers have noted that these substances have anticancer, antibacterial, antifungal, antimalarial, and antiviral properties. As radical scavengers, thiosemicarbazone metal complexes have also been studied. The use of Schiff base metal complexes in the treatment of diseases like antitumor, leprosy, mental disorders, and their enhanced biological activity has been an active area of investigation for the future researchers. They were also found to be active against yeast and act as herbicides, insecticides, rodenticides, and plant growth regulators. The CHN analysis can be used to determine the ligand's composition. In the order to characterize these molecules, 1HNMR and IR spectrum analyses are crucial.

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