

A Therapeutic Journey of Semicarbazide and Thio Semicarbazide Derivatives and their Transition Metals Complexes: Mini Review

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Mini Review

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ABSTRACT

Semicarbazide and Thiosemicarbazide are classes of Schiff bases prepared by condensation between aldehydes / ketones with amines, they belong to urea and thiourea derivatives whose pharmacological activities are a function of attached aldehydes or ketones moiety. Semicarbazide and thiosemicarbazide have potential pharmacological activities including antifungal, anticancer, antibacterial, antimalarial, anticonvulsant, antitubercular, anti-proliferative, anti-inflammatory, antimicrobial, analgesic, antioxidant, radical scavenging, antiviral, and antipyretic properties. Thiosemicarbazides derivatives are of great interest not only in pharmacological activities, but also as the starting material for the preparation of different Schiff base derivatives, metal chelating complexes and anticorrosion agents. This review aims to evaluate the different biological activities of synthesized semicarbazide and thiosemicarbazide derivatives.

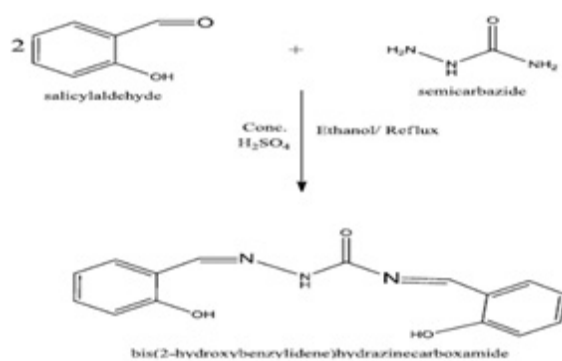
INTRODUCTION

The chelating chemistry has been widely enriched due to the preparation of transition metal complexes, in which the Lewis acid is coordinated through hetero atoms containing free lone pairs of electrons. Metal complexes with Lewis bases containing nitrogen, sulfur and phosphorous donors have been found to have potential pharmacological activities [1,2]. The semicarbazones and thiosemicarbazones usually behave as chelating ligands containing donor imine groups which react with transition metal vacant d-orbital giving complexes. These are multifunctional ligands in both neutral and anionic forms [3]. The complexes can exhibit bioactivities which are not shown by the free ligands. The main interest to prepare and elucidate the structure transition metal complexes of these ligands is due to their pharmacological activities. Some transition metal complexes have different applications such as chemical sensor [4-7], antiviral [8-11] agent and catalyst [12-16]. In addition, they have also been used as antifungal, anticancer, antibacterial, antimalarial, anticonvulsant, antitubercular and anti-proliferative agent. The transition metal complexes based on titanium, gold, cobalt and platinum are used as chemotherapy agents in modern researches [17,18]. Additionally, several nickel (II) complexes with octadienemicarbazones exhibit strong inhibitory activity against *Staphylococcus aureus* and *Escherichia coli*. *In vitro* anticancer studies of several nickel(II) complexes with naphthoquinone semicarbazone and thiosemicarbazone on MCF-7 human breast cancer cells reveal that semicarbazone derivative with nickel(II) complexes is more actively inhibiting cell proliferation than thiosemicarbazone analogues.

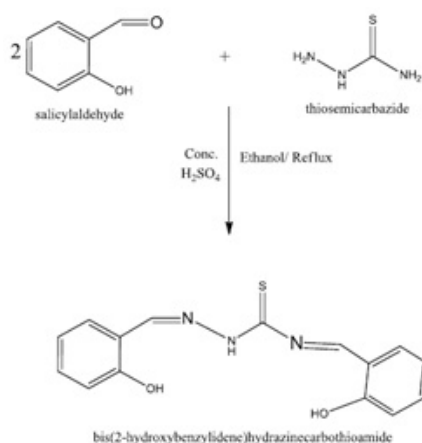
Biological Activities of Different Semicarbazide and Thiosemicarbazide Derivatives

Saddam et al. [19] synthesized Cu(II) complexes with two new Schiff base ligands derived from reaction of salicylaldehyde with semicarbazide (HL₁) and thiosemicarbazide (HL₂) respectively. The synthesized complexes are characterized by IR, UV-Visible, ¹H-NMR and thermal analysis. The structure of the synthesized complexes was distorted square planar (**Figure 1**) and the biological activity revealed that the Cu-HL₂ complex had more antibacterial activity as compared to Cu-HL₁ complex. The metal complexes

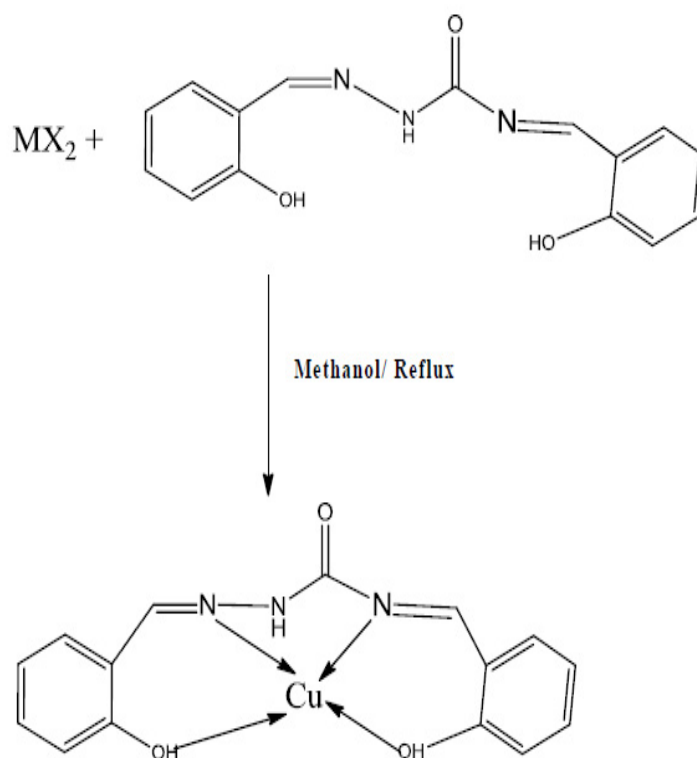
were more antibacterial activity than its free Schiff base ligand.



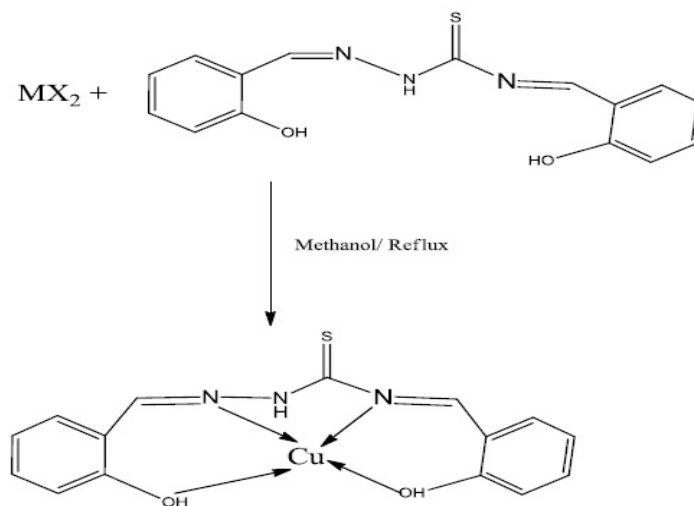
Scheme 1: Synthesis pathway of Schiff base HL¹ (C₁₅H₁₁N₃O₃).



Scheme 2: Synthesis pathway of Schiff base HL² (C₁₅H₁₁N₃O₂S).



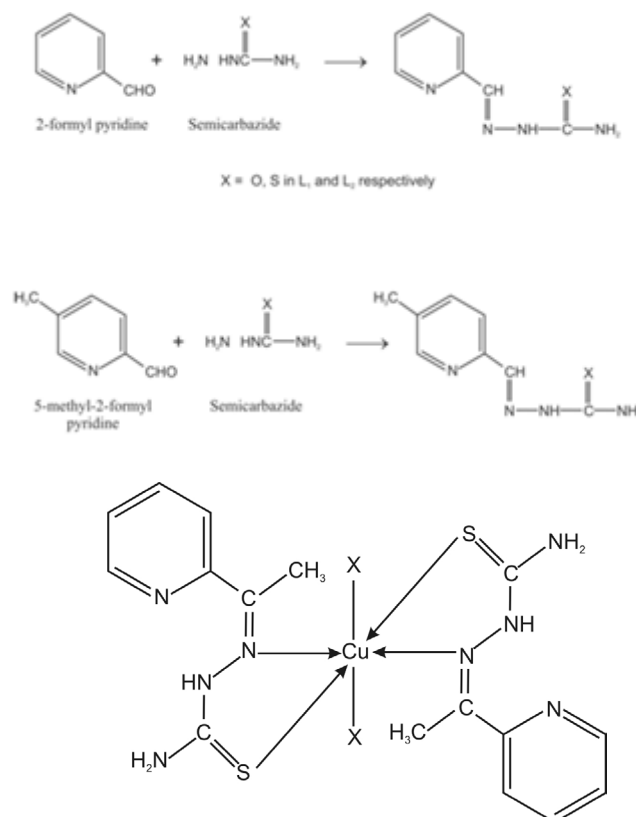
Scheme 3: Synthesis route of [C₁₅H₁₁CuN₃O₃] complex.



Scheme 4: Synthesis route of $[C_{15}H_{11}CuN_3O_2S]$ complex.

Figure 1. Schemes 1, 2, 3 and 4 summarizes the synthesis of HL^1 and HL^2 ligands and their corresponding Cu(II) complexes.

Sulekh et al. [20] synthesized Cu(II) complexes containing 2-formyl pyridine semicarbazone (L_1), 2-formyl pyridine thiosemicarbazone (L_2), 5-methyl-2-formyl pyridine semicarbazone (L_3) and 5-methyl-2-formyl pyridine thiosemicarbazone (L_4). The synthesized complexes were characterized by elemental analysis, FT-IR, 1H NMR, molar conductance, magnetic moment, EPR spectral studies and mass spectrometry. The complexes were found to have general composition $[Cu(L)_2X_2]$ (where $L=L_1, L_2, L_3$ and $L_4, X = Cl^- \frac{1}{2}SO_4^{2-}, NO_3^-$ (**Figure 2**)). On the basis of IR, electronic and EPR spectra of complexes, tetragonal distorted octahedral geometries were found with planar coordination of the ligand around Cu^{2+} ion and the anions occupies axial position.



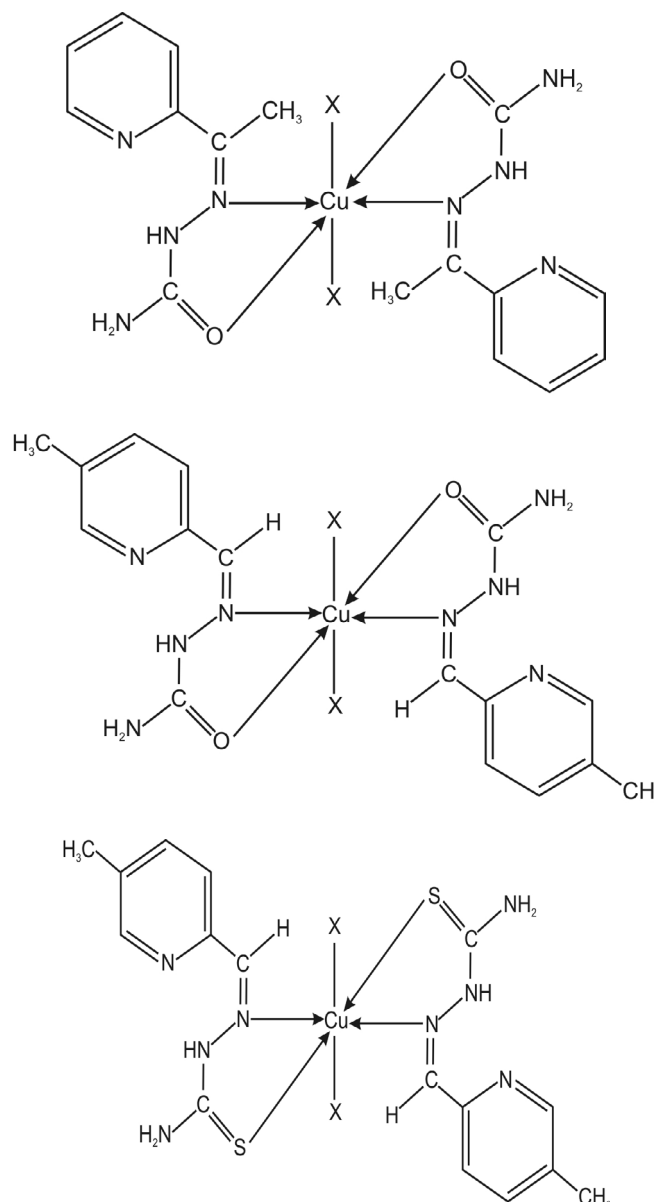
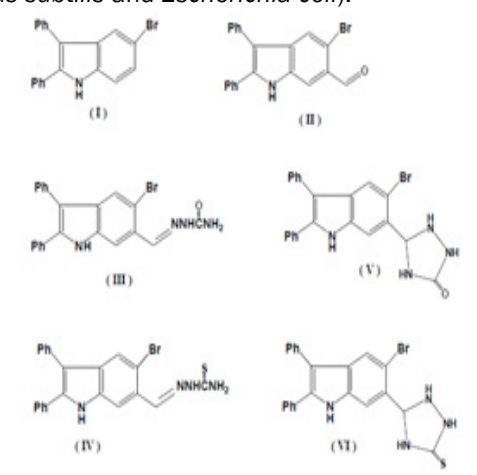


Figure 2. Synthesis of ligands and structure of their corresponding Cu(II) complexes.

Samy et al. ^[21] applied Vilsmier-Haack formylation of 5-bromo-2,3-diphenyl indole afforded 6- formyl derivative which was subjected to various condensation reactions that finally gave heterocyclic rings bounded to the starting compound at position 6 in **Figure 3**. The biological activity for the synthesized compounds revealed that they have antibacterial activity. They have been tested against two types of Bacteria (*Bacillus subtilis* and *Escherichia coli*).



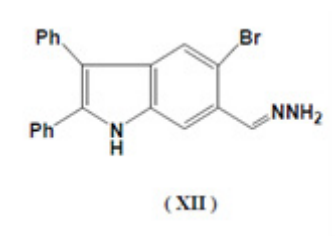
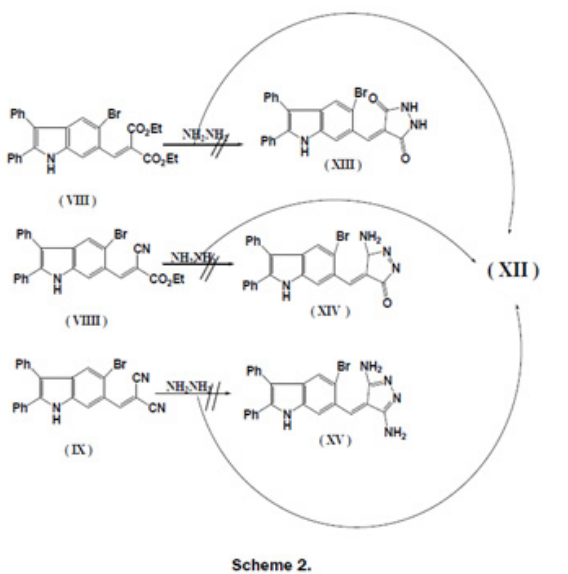
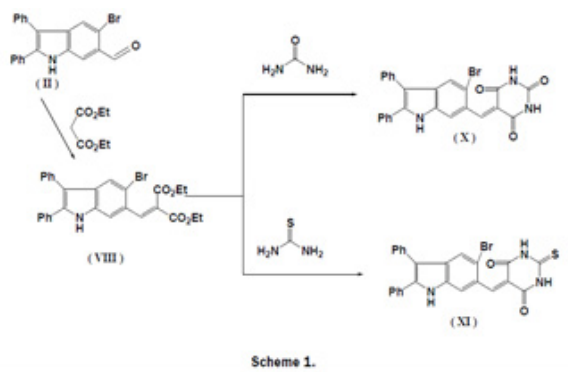
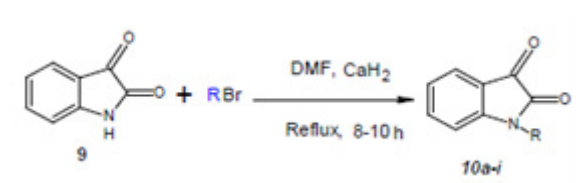


Figure 3. Scheme for condensation reactions of synthesized ligands.

Masoumeh et al. [22] synthesized a series of nine new semicarbazone (12a-i) and six new thiosemicarbazone (14a-c, 14f-h) of isatin which is considered as a vital class of bioactive compounds exhibiting different biological activities. This study showed the synthesis and *In vitro* determination of the cytotoxic and antimicrobial activities of nine new isatin semicarbazones (12a-i) and six new reported thiosemicarbazones (14a-c, 14f-h) (**Figure 4**). They showed that complexes of isatin thiosemicarbazone with metals such as Pd(II), Zn(II) and Hg(II) had enhanced their antimicrobial activities in comparison to their respective ligands [23].



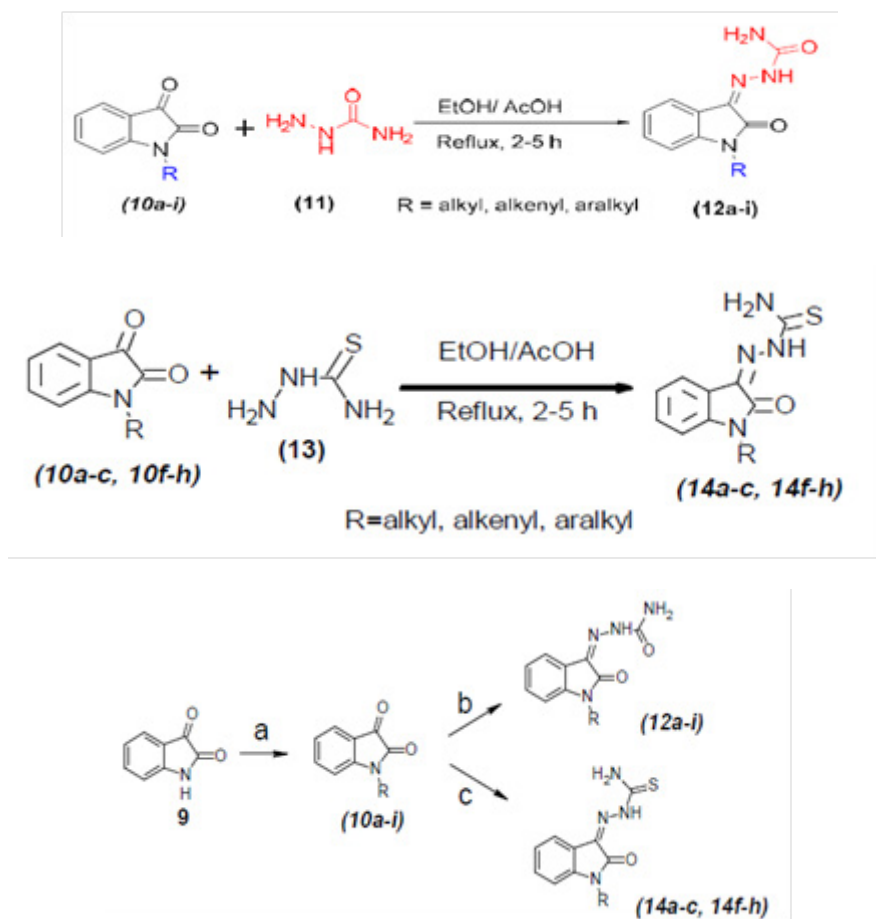
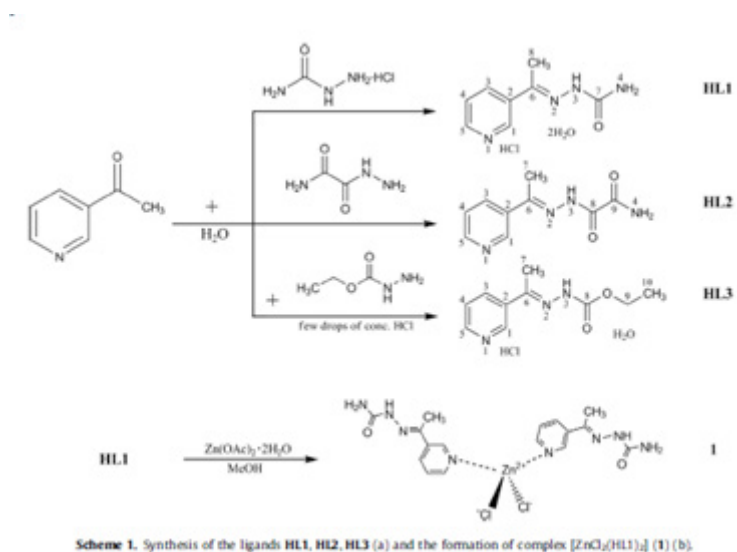


Figure 4. Scheme for condensation reactions of semicarbazide and thiosemicarbazide with isatin.

Božidar et al. [24] synthesized Schiff base complexes based on reaction of 3-acetylpyridine with semicarbazide as well as the corresponding tetrahedral Zn(II). The synthesized complexes were characterized by X-ray crystal structure (**Figure 5**) and spectroscopic methods. The computational studies showed that the ligand coordinated as monodentate although there are several donor atoms. The complex exhibited moderate antibacterial, antifungal and cytotoxic activities while the ligand was mostly inactive. The complex strongly induced formation of reactive oxygen species in tumor cell lines. It also influenced cell cycle progression in tumor cell lines, and induced autophagy.



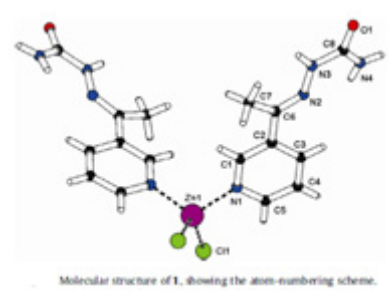
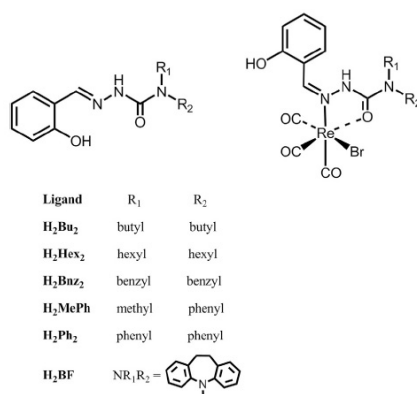


Figure 5. Scheme of reactions of semicarbazide and thiosemicarbazide with acetylpyridine and their corresponding complexes.

Junming et al. [25] synthesized a series of N,N-disubstituted salicylaldehyde semicarbazones (SSCs) and their corresponding rhenium (I) tricarbonyl complexes (**Figure 6**). The synthesized compounds were characterized by IR and ^1H NMR spectroscopy. Crystallographic studies showed that ligands acts as bidentate via its imino nitrogen and carbonyl oxygen atoms. The $[\text{ReBr}(\text{CO})_3(\text{SSC})]$ complexes exhibit moderate to high cytotoxicities towards MOLT-4 cells.



The salicylaldehyde semicarbazones and rhenium(I) carbonyl complexes synthesised in this work.

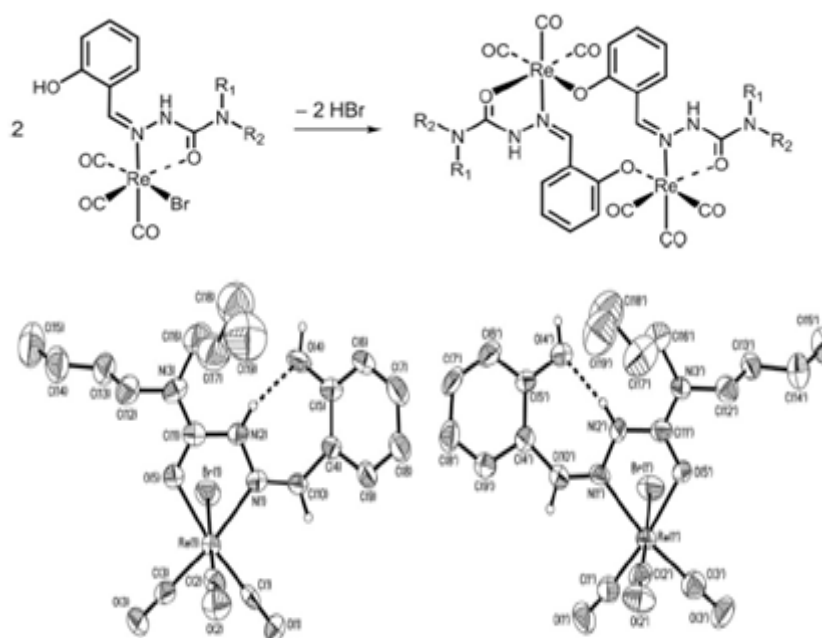
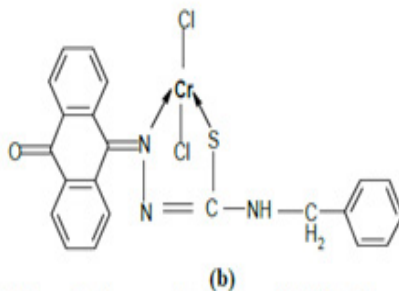
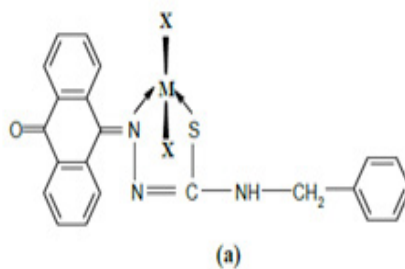


Figure 6. Synthesized ligands and their corresponding complexes X-ray crystal structure.

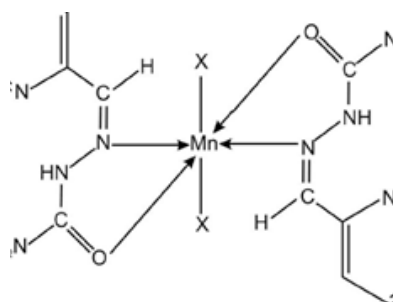
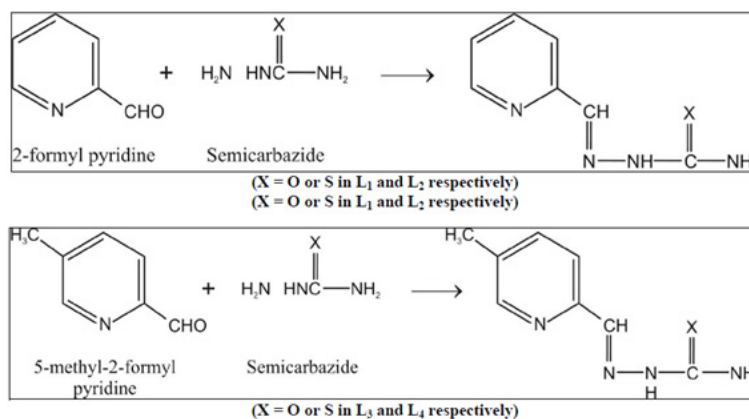
Chandra et al. [26] synthesized a novel Anthraquinone N⁴ benzyl- thiosemicarbazone Cr (III) complex with a potential to act as an anti-cancer drug and characterized by spectral methods (**Figure 7**). Effect of N⁴-substitution, additional donor sites and complexation on the biological activity of the ligand has been studied. The prepared complexes constituted a new family of antibacterial compounds for controlling the growth of at least 1-10 bacterial species. The effect of additional binding sites, N⁴ substitution and complexation with metal ion on biological activity has been given importance.



Scheme I: Proposed structure of (a) Metal complex
(b) Synthesized Anthraquinone N⁴-benzyl 3-thiosemicarbazone Cr(III) complex.

Figure 7. Proposed structure of synthesized ligand and its corresponding complex with Cr(III).

Verma ^[27] synthesized Mn(II) complexes with four semicarbazide and thiosemicarbazide based ligands such as 2-formyl pyridine semicarbazone (L₁), 2-formyl pyridine thiosemicarbazone (L₂), 5-methyl 2-formyl pyridine semicarbazone (L₃) and 5-methyl 2-formyl pyridine thiosemicarbazone (L₄). The prepared ligands and complexes were characterized by elemental analyses, IR, ¹HNMR, mass spectral studies, molar conductance, magnetic susceptibility measurements and spectral studies such as IR, UV-visible and EPR. On the basis of IR electronic and EPR spectral data distorted octahedral geometry of complexes has been suggested (**Figure 8**).



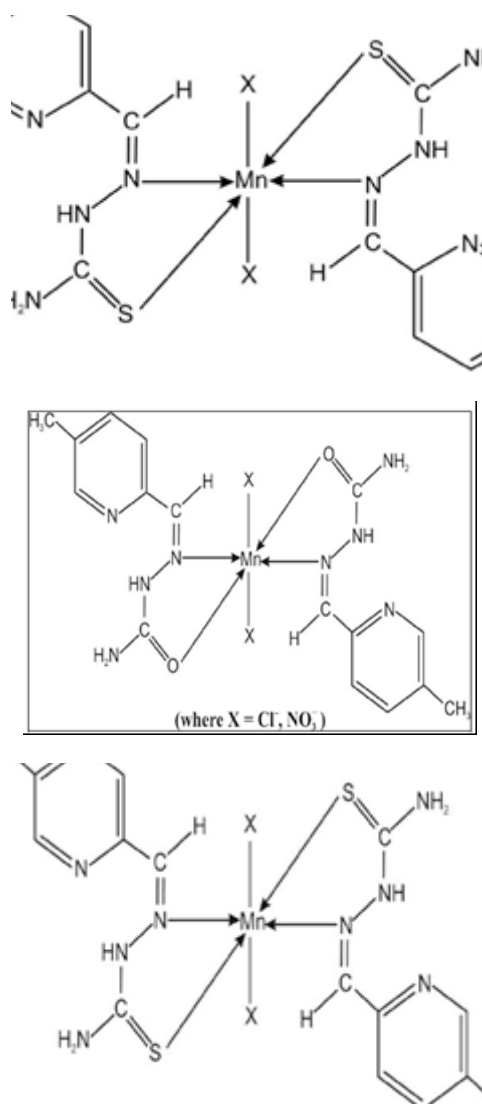
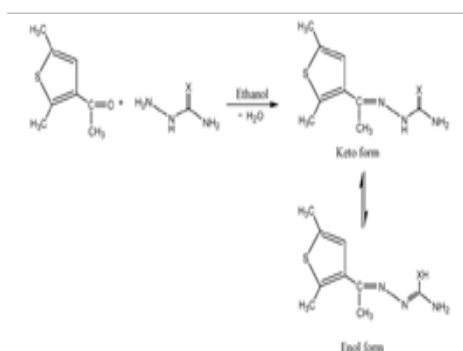


Figure 8. Scheme of synthesized ligands and structure of their corresponding complexes.

Krishna et al. [28] synthesized a new heterocyclic ketimines, 3-acetyl-2,5-dimethylthiophene thiosemicarbazone ($C_9H_{13}N_3OS_2$ or L_1H) and 3-acetyl-2,5-dimethylthiophene semicarbazone ($C_9H_{13}N_3OS$ or L_2H), by reaction of 3-acetyl-2,5-dimethylthiophene with thiosemicarbazide and semicarbazide hydrochloride. The Pd(II) and Pt(II) complexes have been synthesized by mixing metal salts in 1:2 molar ratios with these ligands by using microwave as well as conventional heating method. The structure of these ligands (**Figure 9**) and their complexes has been established on the basis of elemental analysis, melting point determinations, molecular weight determinations, IR, 1H NMR and UV spectral studies. These studies showed that the ligands coordinate to the metal atom in a monobasic bidentate manner and square planar environment around the metal atoms has been proposed to the complexes. The anti-amoebic activity of both the ligands and their palladium compounds against the protozoan parasite *Entamoeba histolytica* has been tested.



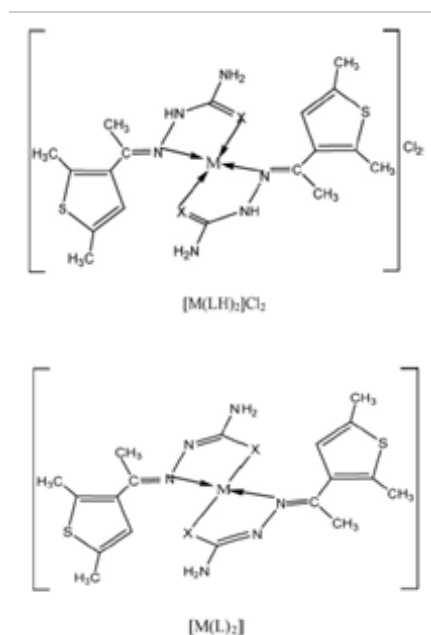


Figure 9. Scheme of synthesized ligands and structure of their corresponding complexes.

CONCLUSION

Semicarbazide and thiosemicarbazide derivatives are related to some necessary biological activities like antitubercular, fungicidal, anthelmintic, antitumor, antibacterial and antimalarial activity. They are found to be physiologically and pharmacologically active. The difficulty of treating microorganism diseases induced to assess the biological activities of metal complexes with different transition metals like Ni(II), Cu(II) and Pd(II). This approach would possibly give compounds with greater biological activity in pharmacological research.

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