# Metal-thiosemicarbazone Complexes - Biological Activity & Structural Studies

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***Abstract:*** **Thiosemicarbazones is an important compounds of N S-donor atoms, that have been several biological properties. Thiosemicarbazones (TSCs) posses antibacterial, anti-viral, anti-tumar and anti-fungal properties. Activity of the N-S ligands influences by the presence of a metal ion.TSCs compounds uses in the extraction and determination of metal ions. Recently synthesis of anti-tumar complexes like cis-platin Pt (II) and Pd (II) chelates with N S-ligands etc., more attention towards the synthesis of these complexes. TSCs complex posses structure dissimilarity, different bonding patterns, potent biological application and ion sensing properties. Present investigation gives detailed description of synthesis, structural studies and biological applications of metal- Thiosemicarbazones chelates. The relations between structural and biological properties of metal N-S ligand complexes of different stoichiometries has been also reviewed.**

***Key words:*** **Metal complex, Thiosemicarbazones, Chelating ligand, anti-microbial activity, anti-tumor properties, anti-viral properties, Heteroleptic ligand etc.**

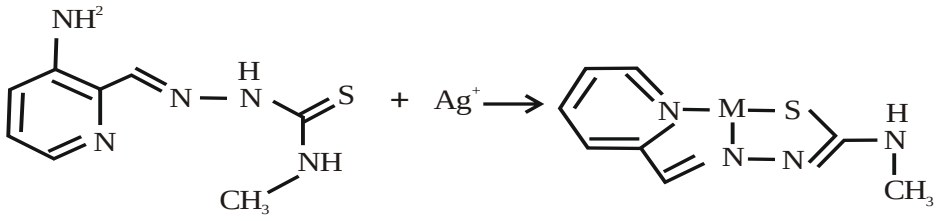
## INTRODUCTION

Thiosemicarbazones and their derivaties are very important complex organic compounds having general formula

$$R - CH_2 - CH = NH - \overset{\overset{S}{\|}}{C} - N - CH_2 - R'$$

They posses anti-bacterial, anti-viral, anti-fungal, anti-cancer and anti-tumor properties, hence wide applications in medicinal, biological and pharmaceutical sectors. TSCs contains N and S-donar atoms, these ligands shows better co-ordination with other groups, proper selection and posses greater stability towards various metal ions. The main scope of present investigation to study the recent research in the fields of synthesis, biological and medicinal importance of Thiosemicarbazones (TSCs) ligands and their metal complexes. The ligand-metal complexes plays important role in living systems because various ligands combine with the same metal moiety. Different ligands shows different properties, which gives potential to the complex and also, increases its activity. Due to the formation of multidentate chelate rings with essential metal ions, TSCs complex shows potent biological action against different diseases. The mostly mechanistic action involves due the liophilic (liquid loving) modification, which regulates the entry to the cell, due to this co-ordination of metal ions is altered. Thiosemicarbazones complex exists is E-form or Z-form and co-ordinate with meal ions as in deprotonated form or as a neutral through N and S-atoms. Brockman et al shows anti-leukemic property of 2-formylpyridine in 19546. French et al predicted the mode of action of the 2-(N)-heterocyclic thiosemicarbazones. Inside the cell, the TSCs complex interacts with vital biomolecules, which leads disruption of cells. TSCs complex posses diversity in structure, variable patterns of bonding, potential towards biological relevance and peculiar ion sensing power.

Transition metals able to aquire various geometries like tetrahedral, octahedral, square planer etc in different environments. TSCs complexes shows variation due to changing substituent groups, aldehydes and ketones, metals ions, solvent, adding molecules on the N and S atoms. TSCs co-ordination with metal ion is show in given figure.

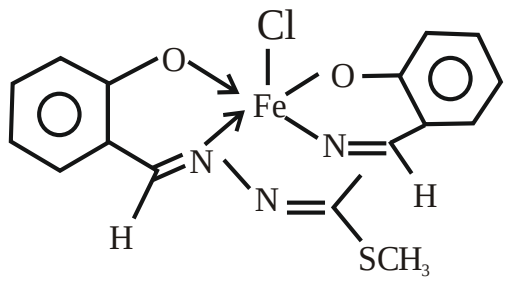


Bonding in TSCs-Metal Complex:

TSCs exist in thione and thiole tautomeric forms in an equilibrium in solution state. Thione from ligand acts in a neutral and bidentate manner, whereas thiol produces negative charge on the bidentate ligand due to removal of proton. The ligand is involved in an uncharged forms with metal complexes. Mostly, but with cobalt, anionic thione form appears. TSCs complex exist in protonated, deprotonated or isomeric forms. In TSCs complex. metal ion-ligand co-ordinates mostly in cis-form. Thiosemicarbazones co-ordinate via thione/thiol S-atom and agomethine nitrogen in a bidentate manner. Thiosemicarbazones complexes properties changes with the modifications in their binding pattern and chelating capacity to the metal atom. Cyclization of some TSCs complexes occurs during experiments. The geometry of the TSCs complex also depends on the ligands, which of affects the biological properties of the complex.

Stereochemistry and Oxidation state of TSCs Complex:

Pearson in 1960s gives HSAB concept for acids and bases. According to HSAB concept oxidation state of metal plays important role in the determination of hard and soft character. Positive oxidation state increases, softness of a metal ion increases. TSCs-metal complex stereochemistry altered by the presence of other donor atoms or groups and charge on the ligand. pH of the reaction medium plays vital role to the reaction. Salicyldehyde 2.



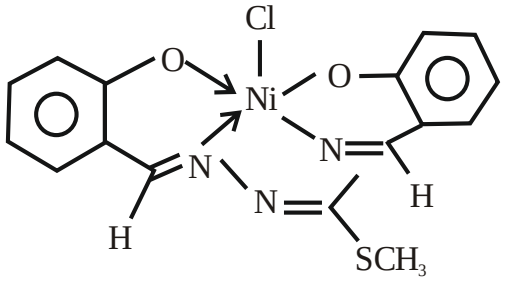

**Fe-Chelate**

Modification in the structure of aldehydes and ketonic carbons the position of thione group co-ordination and position of N-atom in heterocyclic moiety enhances the anti-cancer activity. Copper bis (thiosemicarbazone) complex and bis copper chelates derivatives like glyoxal bis (4-methyl, 4-phenyl-3-thiosemicarbazone) shows potent activity thiosemicarbazones acts as tridentate units negative ligand forming $ML_2$-type complex.

Square planer and octahedral are the most common stereochemistry of TSCs-metal complex. Fe(III), Fe(II), Co(II) and Ni(II) complexes with acetone thiosemicarbazones shows pentadentate characters. Trivalent metal forms $[ML_2]^+$ type complex. $[MLX_2]$ type complex observed in the case of only one reacting ligand. $[ML_2]^{2+}$ type complex observed in the case of Mn. $[ML_2]$ and [MLX] type complexes are synthesized with tridentate ligands. The redox properties in TSCs-metal complex is also an important parameter.

TSCs-Metal Complex Biological Activity:

1. Anti-Cancer Activity : Uncontrolled growth of cells causes cancer and carcinogens is the cancer causing agents cell with slow growth rates shows delay responses to chemotherapy whereas, tumours with high growth rates are more sensitive to chemotherapy. The anti-cancer drugs damages affected cancer cells DNA, inhibiting the new DNA formation and cell replication to stop tumor growth and inhibinb mitosis of the parent cells in to new cells. TSCs-metal complexes acts as anti-cancer agents, whose actiity depends on the tumour cells typology. Substituent position and metal ions gives the cytotoxic activity to the TSCs complex. The Fe or Ni substituted chelates shows maximum cytotoxic activity against K562 ECV304 respectively, shown by several researchers.




**Ni-Chelate**

against cancer cells. Various TSCs-metal complexes shows anti-cancer properties and their activity increases with metal ions and ligands bonding.

TSCs-metal complexes shows anti-cancer activity because-

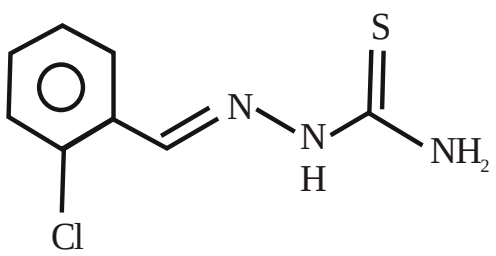
(a) It inhibits the ribonucleotide reductase activity.
(b) It inhibits the topoisomerase activity.

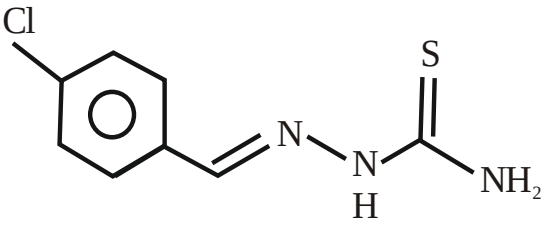
(c) It generates reactive oxygen species and
(d) It inhibits multidrung resistance protein.

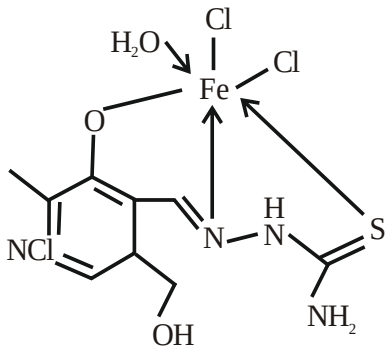
3. Anti-Bacterial Activity of TSCs-Metal Complex:- Different disease caused by pathogens like bacteria, viruses, fungi etc. These diseases treated by anti-biotics, anti-microbial drugs etc, but these compounds shows side-effects to the body in several manners. Now a days some pathogen adopt the drugs environments and generates drug resistance capacity hence, improved drugs can be used to treat drug resistance pathogens. Several TSCs-metal complexes like 2-actylpyridine thiosemicarbazone of Pt(II) and Pd(II) metal ions, benzilbis thiosemicarbazone complexes with Co(II) and Ni(II) metal ions, Cu(II) and Ni(II) complexes with pyridinecarboxaldehyde thiosemicarbazone, chloroform solution of Ag(I) complex of 2-acetypyridine thiosemicarbazone etc, were the effective against bacterial diseases of different strains, confirmed by several researchers.
   TSCs-metal complexes forms chelate rings, these property is studied and researched in pharmaceutical sectors and medicinal sectors, which improves the drugs activity.
4. Anti-typanosomal Activity:- Unicellular protozoans trypanosomes spreads in nature and behaves as a parasites on living beings. TSCs-metal complex behaves as a anti-trypanosomes. Sb(III) complex of thiosemicarbazone tested against tryponosoma cruzi shows greater activity than benzimidazole and nifurtimox explained by several researchers.
5. Anti-malaried Activity of TSCs-metal Complex:- Chimers of ferroquine thiosemicarbazones and aminoquinol thiosemicarbazone atcs as anti-malarial activity Pd(II) complex of 3,4-dichloroacetophenone thiosemicarbazone with ligand was employed against chloroquine-sensitive and chloroquine and pyrimethamine resistant strains. Metal complex shows improved activity than the uncoordinated TSCs.
6. Anti-viral Activity of TSCs-metal Complex:- Isatin-β-thiosemicarbazone and its derivatives shows anti-viral activity against HSV-1 and HSV-2 viruses. Relation between structure and activity shows NH and thiourea groups increases the activity of complex compounds retionoids derived thiosemicarbazones shows potent anti-viral activity. Pd(II) and Pt(II) complexes of TSCs shows selective anti-viral activity.
7. Anti-fungal Activity of TSCs-metal Complex:- Chelation in TSCs-metal complexes shows anti-fungal activity. The lipophilicity of TSCs complexes breaks the permeability barrier of the cell, hence, shows improved activity against fungal diseases. Pt(II) complex of 2-acetylpyridine thiosemicarbazone, dimethylsilicon (IV) complexes of heterocyclic thiosemicarbazones etc. are potent anti-fungal activity.
8. Analgesic and Anti-inflammatory Activity of TSCs-metal Complex:- Isatin thiosemicarbazone, isatin-3-p-chlorophenylimine etc, shows anti-inflammatory activity. Some complexes of TSCs shows analgesic properties, which relatives the pain.
9. Anti-HIV Activity of TSCs-metal Complex :- AIDS is caused by RNA containing retrovirus, which is immune suppressive diseases.

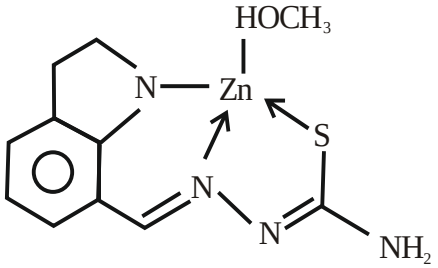
1-[N,N-dimethylaminomethyl] isatin-3-[1'-(6-chlorobenzothiozol-2''-yl)] shows anti-HIV activity for HIV-1 viruses.

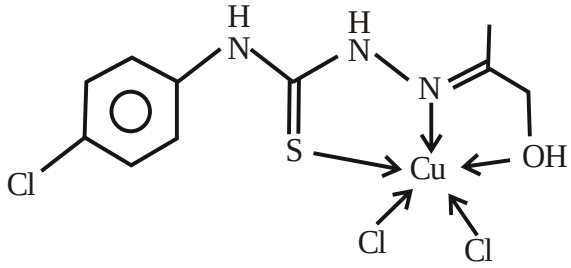
Some important TSCs-metal complexes

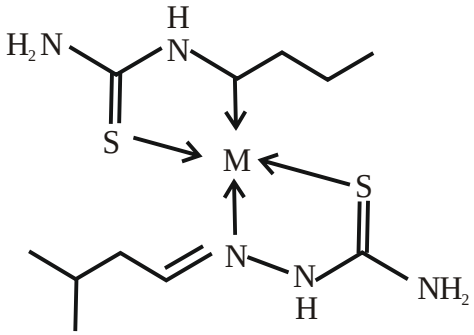





Some TSCs-metal Complex with activity, studied by several researchers

| S.N. | Complex | Metal ions | Activity |
|---|---|---|---|
| 1. | 3-chlorovanillin thiosemicarbazone | Cu(II), Zn((I), Ni(II), and Co(II) | anti-microbial |
| 2. | Indole-7-carbaldehyde thiosemicarbazone | Zn(II), Cd(II), Pd(II) and Pt (II) | cytotoxic |
| 3. | ethylacetoacetate bis (thiosemicarbazone) | Cr(III), Mn(II), Co(II), Ni(II), Cu(II), Zn (II) and Cd(II) | anti-tumor and antimicrobial properties |
| 4. | Proline-2-formylpyridine thiosemicarbazone | Cu(II), Zn(II) and Ni (II) | anti-proliferate activity |
| 5. | 2,6-pyridinedicarboxy aldehyde thiosemicarbazone | Cr(III), Co(II), Ni(II) and Cu(II) | antimicrobial |
| 6. | 3-methylbutanal thiosemicarbazone | Co(II), Ni(II), Cd(II), Hg(II), Fe(III), Zn(II) and Cu(II) | antibacterial |
| 7. | terepthalaldehyde thiosemicarbazone | Cu(II) and Zn (II) | anti-bacterial |
| 8. | 3-acetyle or 4-acetyl | Ni(II), Co(II) and Cu(II) | anti-cancer |
| 9. | 3-5-diacetyl-1,2,4-triazole bis (4-N-isopropyl thiosemicarbazone) | Pt(II) | anti-tumor |
| 10. | (E)-1-(1-hydroxypropane-2-ylidene) thiosemicarbazone | Co(III), Ni(II), Zn(II) and Cu(II) | anti-microbial |

Dinuclear TSCs complexes also studied these complex having complex structures and contain metal-metal bonds which affects magnetic behaviour of the complexes. Homo and heteronuclear complexes of TSCs shows biological activity against pathogens.

## CONCLUSIONS

TSCs-metal complexes contains NS-donor atoms, possess anti-microbial, anti-bacterial, anti-fungus, anti-viral and anti-tumor activity. Metal ion in influence the activity of N and S-ligands. Cis-platin is an important anti-cancer compound. The most interesting features of the TSCs complexes are structural dissimilarity, different bonding patterns, several biological applications and ion sensing properties. The addition of metal ion to the complex gives redox properties, which are useful in biological reactions. Different geometries are obtained due to different co-ordination modes, which modified and controlled to help in biological

binding at different receptors. Due to chelation complex crosses cell membrane by diffusion these properties make the binding of the complex with the receptor molecules. Present investigation gives structural studies, synthesis and biological applications of TSCs-metal complexes. Relationship between structure and biological activity of the TSCs-metal complexes of different stoichiometries has been also reviewed.

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