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TRANSITION METAL COMPLEXES OF THIOSEMICARBAZONES: STRUCURE AND BIOLOGICAL ACTIVITY

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Abstract: **Thiosemicarbazones are the compounds that show antiviral, antibacterial, antifungal, anti-inflammatory and anticancer properties. When these compounds are complexed with transition metals, the biological activity of ligand is enhanced. The most relevant papers recently published are reviewed with an attempt to determine structural correlations between transition metal ion complexes of thiosemicarbazones and their wide spectrum of biological applications.**

Keywords: **Thiosemicarbazones, bioactive, transition metal complexes, biological activity.**

1. INTRODUCTION

Thiosemicarbazones is a class of compounds obtained by condensing thiosemicarbazide with suitable aldehydes or ketones. The active grouping for chelation is Sulphur. In most of the complexes, the thiosemicarbazones coordinate to the metal ion as a bidentate ligand bonding through the sulphur atom and the hydrazino nitrogen atom. In a few cases they behave as unidentate ligands by bonding only through the sulphur atom. In certain cases thiosemicarbazones also act as multidentate ligands if donor groups are also present in the parent aldehyde or ketone moiety.

Thiosemicarbazones are an important class of N, S donor ligands which have considerable interest because of their chemistry and biological activities, such as antitumor, antibacterial, antiviral, antiamoebic and antimalarial activities (1, 2).Thiosemicarbazones have been studied for a considerable period of time for their biological properties. Traces of interest date back to the beginning of the 20th century but the first reports on their medical applications began to appear in the Fifties as drugs against tuberculosis and leprosy (3, 4). In the Sixties their antiviral properties were discovered and a huge amount of research was carried out that eventually led to the commercialization of methisazone, Marboran ® to treat smallpox (5). In this period one of the first antitumor activity results was published (6). Recently Triapine (3-aminopyridine-2carboxaldehydethiosemicarbazone) has been developed as an anticancer drug and has reached clinical phase II on several cancer types (7, 8). Presently, the areas in which thiosemicarbazones are receiving more attention can be broadly classified according to their antitumor, antiprotozoal, antibacterial or antiviral activities and in all cases their action has been shown to involve interaction with metal ions (9, 10). This review will be mainly focused on the most relevant papers published in the past ten years since an extensive report by Beraldo et al. (11) covers the previous works.

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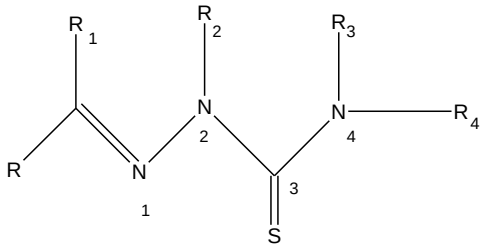
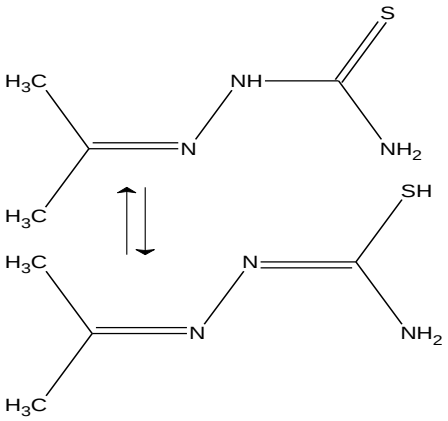
2. CHEMISTRY

According to the IUPAC nomenclature (12), thiosemicarbazones, which are usually obtained by condensation of an aldehyde or ketone with thiosemicarbazide, may be named by adding the class name "thiosemicarbazone" after the name of the condensed aldehyde or ketone. In the same way bis(thiosemicarbazones) are derived from dicarbonyl compounds and two thiosemicarbazides moieties. The basic structure of thiosemicarbazone compounds and IUPAC numbering scheme is shown in Scheme **1**.



Scheme 1. The drawing represents the general formula for thiosemicarbazones. R, R_2 , R_3, R_4 = H , or any organic substituent (the conventional numbering scheme from 1 to 4 is shown).

The thiosemicarbazides used in the synthesis can be obtained by a series of synthetic procedures. For examples the reaction of hydrazine hydrate with isothiocyanates or the reaction of amines with carbon disulphide followed the addition of hydrazines hydrate (13). In general, the synthesis of thiosemicarbazone compounds presents low cost and high atoms economy since all the atoms from the reagents (except water librated in the condensation) are present in the final molecule. Looking at the structural characteristics, thiosemicarbazones contain a rich set of donor atoms and are well known chelators of metal ions. The coordination chemistry of thiosemicarbazones appear to be very interesting from the point of view of both the number of metals forming complexes with them and the stabilization of various (less common) oxidation states of metals. Moreover many of their biological activities of the thiosemicarbazones often have been attributed to their ability of chelation with endogenous metals (14). Thiosemicarbazone ligands may exist as thione/thiol tautomeric forms owing to the intramolecular proton transfer, Scheme 2.



Scheme 2: Tautomeric forms of thiosemicarbazones

A review of thiosemicarbozone structures (15) shows that in solid state these molecules are almost planar, with the sulphur atom *trans* to the azomethine nitrogen atom (configuration E). Although there are several electronic and steric factors that may contribute to the adoption of this arrangement, the most important is probably that the *trans* arrangement places the amine (4N) and azomethine (1N) nitrogen atom in relative positions suitable for intramolecular hydrogen bonding. However in the most of the complexes the thiosemicarbazones moiety coordinates to the metal ion in the *cis* configuration through the thione/thiol atom and the azomethine nitrogen atom. The coordination capacity of thiosemicarbazones can be further increased, if the parent aldehyde or ketone contains additional functional groups in the position suitable for chelation. Particularly, compounds in which the thiosemicarbazones side chain is attached in position to an N-hetrocyclic thiosemicarbazones have shown substantial activity against various human tumour lines. The (N)-TSCs possess a conjugate NNS donar set which favour the coordination to metal ions forming two five membered chelate rings of a partially conjugate

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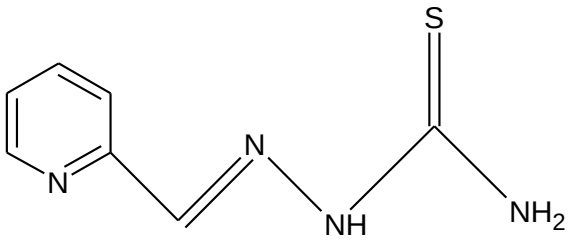
character and these particular structural characteristic seems to be essential for biological activity (16). Therefore the modification of the structure of (N)-TSC derivatives gives the possibility of synthesizing novel compounds and exploring their biological activities.

3. BIOLOGICAL ACTIVITY

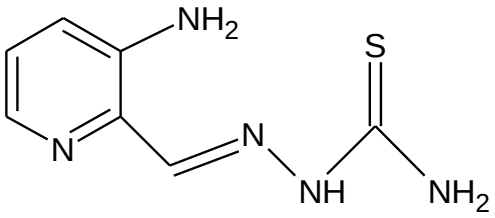
3.1. ANTICANCER ACTIVITY

Thiosemicarbazone compounds are being used as anticancer agents from a long time. Their anticancer activity is very much depends on the typology of tumour cells. Ribonucleotide reductase is an iron-dependent enzyme that promotes the reduction of ribose to deoxyribose through a free radical mechanism that is triggered by a tyrosyl radical. Inhibition of this enzyme leads to a block in the synthesis phase of the cell cycle and eventually to cell death by apoptosis. The antitumor effect of thiosemicarbazones was reported first in the Sixties. The anti-leukemic effect of 2-formylpyridine thiosemicarbazone (Scheme **3**) was first reported by Brockman *et al*. (17).



Scheme 3: 2-formylpyridine thiosemicarbazone

Triapine (3-amino-2 formylpyridine thiosemicarbazones) is a potent proliferation inhibitor of many cancer types and presents a marked selectivity for tumour cells. Triapine (Scheme **4)** is currently in phase II clinical trial on many typologies of tumours (7, 18, 19).



Scheme **4:** 3-amino-2 formylpyridine thiosemicarbazone

Marc-Andre leblanc et al. (20) synthesized Zinc, Cobalt, and Copper Complexes of 1-(Naphthalene-2-yl)ethanonethiosemicarbazone and reported anticancer activity of the complexes against a panel of human colon cancer cells (HCT-116 and Caco-2). The compounds bind to DNA via an intercalative mode with binding constants of 9.7×10^4 M^{-1}, 1.8×10^5 M^{-1}, 9.5×10^4 M^{-1}, for the zinc, cobalt, and copper complexes, respectively. They related cytotoxicity of the complexes to the DNA binding as if the anticancer activity of the complexes is not comprehensively related to the interaction with DNA, the complex with the lowest *in vitro* activity has the highest DNA binding constant. Kowol et al. (21, 22) have reported the synthesis, characterization and biological activities of complexes of Fe (III) and Ga(III). They tested *in vitro* antiproliferative activity of 2-acetylpyridine N, N-dimethyl thiosemicarbazone, 2-acetylpyridine N-pyrrolidinyl thiosemicarbazone, acetylpyrazine N,N-dimethyl thiosemicarbazone, acetylpyrazine N-pyrrolidinyl thiosemicarbazone, acetylpyrazine N-piperidinyl thiosemicarbazones and complexes of 3-amino-2formylpyridine (Triapine), 2-formylpyridine, 2-acetylpyridine, 2-pyridine formamide thiosemicarbazones as well as their N4-dimethylated analogues on two human cancer cell lines (41M and SK-BR-3). They resulted increased cytotoxicity of gallium (III) complexes and reduced cytotoxity of iron (III) complexes compared to the metal-free thiosemicarbazones.

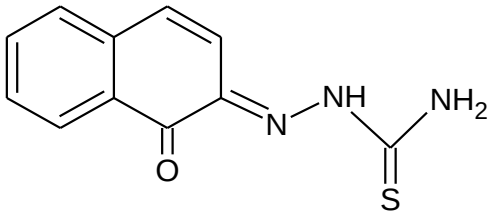
Sarmistha Halder et al. (23) has synthesized a series of mixed ligand complexes of Palladium viz. $[Pd(L^1)(pph_3)]$ and $[Pd(L^2)(pic)]$, {where L^1 = salicylaldehyde thiosemicarbazone, L^2 = 2-hydroxyacetophenone thiosemicarbazones and pic = 4-picoline } and screened these complexes for in vitro cytotoxicity along with four human clinical drugs viz. Cisplatin,

BCNU, 5-fluorouracil (5-FU) and hydroxyurea in two human tumor cell lines, namely promyelocytic leukemia HL-60 and histiocytic lymphoma U-937 and it was found that crystal [Pd(L)] showed the lowest IC_{50} value and was found to be much more cytotoxic than the reference anticancer drugs in both the cell lines. An apoptosis study in HL-60 with [Pd (L^2) $(pph)_3$] resulted that at 10 mm concentration it induces apoptosis to a greater extent than cisplatin and camptothecin .

Mendes *et al*. (24) has studied the cytotoxic activity of 2-pyridineformamide thiosemicarbazones and its N_4-ethyl derivatives and of their gallium (III) complexes against malignant glioblastoma RT2 and T98 cell lines. These compounds were found able to induce cell death by apoptosis. The gallium(III) complexes of the 4-methyl and 4-ethyl derivatives showed IC_{50} values in the 0.81-9.57 µm range against RT2 cells and in the 3.6-11.30 µm range against T98 cells and were found 20-fold more potent than cisplatin.

Anti-proliferative activity of complexes of thiosmicarazones against tumour cells has been reported in recent years. 2'-Benzoylpyridine thiosemicarbazones (bpt) are effective iron chelators and display potent anti-proliferative activity against tumour cells. Recently Adeline Y. Lukmantara et al. (25) reported structure–activity relationship of 4-phenyl-substituted 2'-benzoylpyridine thiosemicarbazones (bpt) with potent and selective anti-tumour activity. They have synthesized ten analogues containing phenyl substituents at the N4-position of the bpt structure and found that these compounds demonstrate significant enhancement in anti-proliferative activity compared to the clinically used iron chelator, desferrioxamine (DFO). Furthermore, the compounds showed appreciable therapeutic indices against cancer cells over normal cells in vitro. Structure–activity analysis revealed that electron-donating substituents such as $–CH_3$ and $–OCH_3$ resulted in greater anti-proliferative activity than electron withdrawing groups such as –Br and –Cl. They examined the effect of complexation on the anti-proliferative behaviour of the Bp4(R)pt chelators against SK-N-MC neuroepithelioma cells and found anti-proliferative activity of iron complexes against tumour cells 3- to 300-fold less potent compared to the respective free ligands and all of the iron complexes showed IC_{50} values of >0.43 µm while their free ligands had IC_{50} values <0.12 µM. These results help to elucidate the effect of a variety of 4-phenyl substituents on the biological activity of BpT series of chelators and facilitate the future development of thiosemicarbazones with improved anti-tumour activity.

Copper-thiosemicarbazone complexes have significantly higher growth inhibitory activity than the uncomplexed ligand and have lower IC_{50} values against tumour cells than other reported topoisomerase-II inhibitors (26). The antitumor activity of 1, 2-naphthoquinone-2-thiosemicarbazone (Scheme **5**) and that of its metal complexes of copper (II), palladium(II) and nickel(II) was investigated by Chen *et al*. (27) against MCF-7 human breast cancer cells. The results revealed that these complexes are effective antitumor chemicals in inhibiting MCF-7 cell growth. The nickel complex is the most effective among the complexes studied and based on IC_{50} values it is also more effective than etoposide, a commercial antitumor drug. Snehalkumar D. Patil et al. (28) also reported improvement in anticancer activity of thiosemicarbazone when these are complexed with copper (II) against *M. Tuberculosis.*



Scheme **5:** 1, 2-naphthoquinone-2-thiosemicarbazone

Ruthenium complexes have attracted larger attention in the last 20 years as potential antitumor agents and also as antibacterial agents. Ruthenium compounds are regarded as promising alternatives to platinum compounds and offer many approaches to innovative metallopharmaceuticals. Kalyani P. et al.(29) have reported Synthesis, characterization and nuclease activity of Ru (III) complexes of isatin thiosemicarbazone (Is.Tsc) and substituted thiosemicarbazones on pBR 322 plasmid DNA by agarose gel electrophoresis in the presence/absence of H_2O_2, the nuclease activity was greatly enhanced by incorporation of metal with ligands.

Anticancer potential of n(4)substituted 5-nitroisatin thiosemicarbazones and their copper(ii) complexes have been studied by N. K. Singh et al. recently(30). N(4) modified copper thiosemicarbazones have been extensively studied for their anticancer potency toward various cancer cells as they exhibit less toxicity, wide spectrum of activity, non-resistance

behaviour and a novel mechanism of action as compared to that of platinum complexes. 5-Nitroisatin -4-thiomorpholinyl-3-thiosemicarbazone(L1), 5-nitroisatin -4, 4-dimethyl-3-thiosemicarbazone(L2), and their copper (II) complexes; CuL1 and CuL2 were prepared and characterized by elemental analysis. All the compounds were screened against breast cancer (MCF-7 and MDA-MB-231), skin cancer (A431) and normal prostate cell line (PNT2) in terms of cell viability and found that all the synthesized compounds exhibited in vitro antiproliferation toward the tested cancer cells. These complexes were found to be more effective on MDA-MB-231 than on A431 and MCF-7 cells.

3.2. ANTIBACTERIAL ACTIVITY

Thiosemicarbazones and their transition metal complexes have been found to have excellent antibacterial activities**.** The main targets for antibacterial activity are inhibit synthesis of peptidoglycan, alter the microbial cytoplasmic membrane, alter translation and inhibit nucleic acid replication by blocking topoisomerases and inhibit transcription (31). Affan et al. studied antibacterial activity of organotin (IV) complexes of 2-hydroxyacetophenone-N(4)-cyclohexyl thiosemicarbazone against *E. coli, Enterobacter aerogenes, S. aurues* and *Salmonella typhi* and their results showed that the organotin complexes have better activity than the free ligand. Among the organotin complexes, diphenyltin (IV) derivatives exhibits significantly better activity than the monoorganotin (IV) derivatives (31). Sandeep Kumar et al. repoted that transition metal complexes of thiosemicarbazone has effective antimicrobial activity than free thiosemicarbazones (33). Shim et al. recently reviewed the biological applications of thiosemicarbazones and their metal complexes and they found that in most cases the biological applications were enhanced by chelating the thiosemicarbazones with the metal ions (34).

Recently Neeraj Sharma has synthesized some mononuclear complexes $[ML_1L_2(NO_3)_2]$ {where M = [Co(II), Ni(II), Cu(II) and Zn(II)], L_1 = 2- Hydroxy-5-nitrobenzaldehyde and L_2 = β - diketones (Pentane-2,4-dione, 1 phenylbutane-1,3-dione, 1,3diphenylpropane-1,3-dione)}, and found octahedral geometry of Co(II), Ni(II), Cu(II) and Zn(II) metal complexes. The relative antimicrobial studies of different mixed ligand metal complexes shows that Cu (II) complex is more effective and toxic compared to other complexes towards gram positive bacteria like *S. Aureus* (35). Manimaran Arumugam et al. (36) have synthesized hexa-coordinated binuclear Ru(II) thiosemicarbazone complexes of the type $\{[(B)(EPh_3)(CO)ClRu]_2L\}$ (where, E = P or As; B =PPh_3 or $AsPh_3$ or pyridine; L = mononucleating NS donor of N-substituted thiosemicarbazones). These binucleating thiosemicarbazone ligands and their Ru(II) complexes were also screened for their antibacterial activity against *Klebsiella pneumoniae, Shigella sp., Micrococcus luteus, Escherichia coli* and *Salmonella typhi*, and it was found out that the activity of the complexes almost reaches the effectiveness of the conventional bacteriocide. Recently Devesh Kumar et al. (37) reviewed pharmacological actions such as, anticonvulsant, antidepressant and other biological activity of metal complexes of schiff base with special reference to thiosemicarbazone derivatives.

M. Jagadeesh et al.(38) has synthesized three chalcogenic thiosemicarbazones (3,4-difluoroacetophenonethiosemicarba zone(**1**), 2-bromo-4'chloroacetophenone thiosemicarbazone(**2**) and 2, 4'-dibromoacetophenone thiosemicarbazone(**3**) by using a conventional one step processes in which the respective halo-substituted acetophenones are condensed with thiosemicarbazide to result in the formation of the product. The chalcogenic thiosemicarbazones then tested for their antimicrobial activity against some human pathogens like *E. coli*, *B. subtilis*, *P. aureginosa* and *S. aureus*. The antimicrobial activity studies suggested that the compounds were potential agents of biological importance. Among all the compounds tested the fluoro substituted compound was found to be more active than the remaining compounds.

Vinod K. Sharma et al. (39) reported synthetic, spectroscopic, and biological studies of sixteen ring-substituted 4-phenylthiosemicarbazones and 4-nitrophenyl- thiosemicarbazones of anisaldehyde, 4-chlorobenzaldehyde, 4-fluorobenzaldehyde, and vanillin with ruthenium (III) and rhodium (III) chlorides. The complexes were screened against *Bacillus subtilis* and *Pseudomonos aeruginosa* and toxicity of the complexes was found better than parent ligand owing to the chelation theory of Tweedy (40). They revealed that the variation in the toxicity of different complexes against various organisms depends either on the impermeability of the cells of the microbes or differences in ribosome in microbial cells (41). The enhanced effect of complexes due to chelation could increase the lipophilicity of the central metal atom, which favours the permeation through the lipid layers of the cell wall. On the other hand, the mode of action of the compounds may involve the formation of hydrogen bonds through azomethine group of the complexes with the active centres of cell constituents resulting in the interference with normal cell process.

Recently Nimya A. Mathews and M.R. Pratapchandra Kurup(42) repoeted In vitro biomolecular interaction studies and cytotoxic activities of copper(II) and zinc(II) complexes bearing ONS donor thiosemicarbazones. The DNA binding ability

of the complexes was studied using absorbance and fluorescence spectroscopic technique. Complexes bind effectively to DNA in the order 105 M−1 through intercalative mode of binding. The DNA cleavage ability of the complexes showed that complexes cleaved DNA without an oxidizing agent. Further molecular docking confirmed the binding affinity of the complexes with DNA. It has been established that the total hydrophobicity of the ligand system directed by the substituent existing in the ligand part of the metal complex plays a critical role in the DNA binding, cleavage, and anticancer properties. Thus, when the base is a phen ring rather than a bipy ring, there is an enhancement in the DNA binding ability. The in vitro cytotoxicity of 1 and 2 complexes against a human breast cancer cell line (MDMBA-231) exhibits lower antitumor activity for Complex2 compared that of Complex 1. This result agrees well with their DNA binding abilities. Thus, our complexes showed relevant biological activities targeting DNA and thus giving new potential anticancer drugs with useful reference.

Recently Mohammed B. Hussein et. al.(43) reported antimicrobial activity of 4-imidazolecarboxaldehyde thiosemicarba zone and its Pt(II) and Pd(II) complexes. An in vitro antimicrobial investigation was carried out for the free ligand and its metal complexes against *staphylococcus aureus*, *Escherichia coli* and one fungi *Candida albicans*, and found that complexes shows higher activity than free ligand.

3.3. ANTIVIRAL ACTIVITY

The antiviral activity of thiosemicarbazones was reported first in 1950 by Hamre et al. (42) who found that derivatives of benzaldehyde thiosemicarbazone were active against neurovaccinial infection in mice when given orally. This prompted further investigation of other thiosemicarbazones. Charles Shipman et al. (44) have evaluated a series of 111 thiosemicarbazones of 2-acetylpyridine, 2-acetylquinoline, 1-acetyl-isoquinoline, and related compounds as inhibitors of herpes simplex virus in vitro and in a cutaneous herpes guinea pig model. All derivatives tested were potent inhibitors of virus replication with mean 50% inhibitory concentrations of 1.1~tg/ml for both type 1 and 2 herpes simplex virus.

4. CONCLUSION

Thiosemicarbazones and their transition metal complexes present a wide range of bioactivities and their chemistry and pharmacological applications as anticancer, antibacterial, antiamoebic, antimalarial and antiviral agents have been extensively investigated. The biological properties of thiosemicarbazones are often related to metal coordination as in most cases the biological applications were enhanced by chelating the thiosemicarbazones with the metal ions, but their mechanisms were not fully discovered. So it is still needed to explore the potentiality of thiosemicarbazones and their metal complexes.

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