Coordination Complexes of Copper, Silver and Gold with SNO Group Containing Thiosemicarbazones Schiff Base Ligands and their Biological Applications

[1, 2]Md. Mohiuddin and [1]Md. Azharul Arafath*
[1]*Department of Chemistry, Shahjalal University of Science and Technology, Sylhet 3114, Bangladesh.*
[2]*Department of Chemistry, Shahjalal Mohabiddaloy, Jagannath Pur, Sunamgonj, Bangladesh.*
arafath-che@sust.edu*

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Summary: The thiosemicarbazone Schiff base ligand is very important segment for chemistry, more specifically coordination chemistry. These compounds and their complexes widely used as medicinal agents for different lethal diseases such as cancer and other contagious disease caused by bacteria. The coordinated metal (coinage) complexes exhibited higher activities than free ligand for all the biological investigation of anticancer and antibacterial activities. The TSCs ligands having polydentate S-N-O coordinating sites. The mode of coordination of these ligands is flexible, it can act as tridentate or bidentate ligand. These ligand form mostly square planar complexes with copper, silver and gold metal ions. This research content could guide to identify the synthesized biomaterial. In this review, copper, silver, gold complexes are comprehensively summarized, and their activities and mechanism are documented. This review will provide very cut-edge guide of TSCs and their complexes to use in different field.

Keywords: Thiosemicarbazone Schiff base; Coinage metals; Coordination complexes; Cytotoxicity; Antibacterial activity.

Introduction

Schiff base is one the important segments for both chemistry and medicinal chemistry, which receive extensive attention from the researchers. Primary amines react with aldehyde or ketones to form products by condensation was first invented by Hugo Schiff in 1864 (Scheme-1) [1].

Schiff base and their coordination complexes are significant segment of coordination chemistry. Many Schiff bases and their complexes of transition metals showed biological and pharmaceutical applications [2, 3]. These ligands contain a soft atom (sulfur) along with hard atoms (nitrogen and oxygen) in same molecule [4]. Schiff bases chelate with donor sites sulfur, oxygen, and nitrogen sites with metal ions. These complexes could be used as medicines for different diseases caused by fungi, virus and bacteria as well as against cancer [5-9]. Aromatic aldehyde forms stable Schiff bases with an active conjugation system, where aliphatic aldehydes are unstable and gladly polymerize [10]. TSCs and their metal complexes application is significantly increased owing to their metal-complexes biological activities as antitumor, anticancer, antiviral, and antimalarial agents [11-18]. TSCs has contained multi-donor NSO features provide orientation of sulfur and nitrogen atoms in their molecular backbone which shows high coordination usefulness and auspicious physiochemical properties [19-20].

Copper Complexes with thiosemicarbazone Schiff base compound

Copper complexes use as various tonic resolves such as antimalarial, antibacterial and antifungal agent, neuroprotective action in Alzheimer's disease, diabetes, inflammatory states, cardiovascular diseases and skin wounds [21]. Klayman *et al*. reported that many TSCs ligands complexes have vast application as medicinal agent against leprosy [22], viral infections [23-25], tuberculosis [26], psoriasis [27], malaria [28-30] and trypanosomiasis reported in 1981. Douglas *et al*. have been reported in 1970 Copper (II) chloride react with Pyruvic acid thiosemicarbazone, (H, Pyrutsc), to formulae copper(II) complexes, [Cu(HPyrutsc)X].nA, where A= preparative (e.g. methanol), n = 0, 1, 2 and X =monobasic anion [31]. Copper(II)bis(thiosemi carbazone) complexes reaction through intracellular sulfhydryl groups and this complexes are reductively decomposed was reported by D. H. Petering *et al*. in 1972 [32-34]. The tetragonally distorted octahedral complexes, $[Cu(HTSC)_2X_2]$ (X = Br, Cl, NO_3 or ClO_4) of l-(α)-furyl-4-benzylamidothiosemicarbazone and 4-benzylamido thiosemicarbazone was reported by Jain *et al*. 1977 [35]. Salicylaldehyde-S-methyl thiosemicarbazones react with copper(II) chloride to form copper complexes of sort [Cu(HL)X]. nH_2O (where X = Br, Cl, NO_3, or ClO_4) was reported by D. petrovic *et al*. in 1978 [36]. V.M. Leovats *et al*. have reported that presence of sulfur atoms ease in

*To whom all correspondence should be addressed.

coordination to form complex. They occupy square planar structures in which phenolic oxygen atom, the terminal amide nitrogen atom and hydrazinic nitrogen atom are occupied three of the coordinating sites was reported in 1978 [37]. Jain *et al*. also suggested square planer geometries for copper(II) complexes of α-pyridylthiosemicarbazone derivatives on the basis of electronic spectral bands and magnetic moments. The ligand and the coordinating sites containing bidentate nature (thione sulfur atoms and pyridyl nitrogen atoms) and the ligand obligate recognized going on the base of frequency changes of conforming immersions in the IR bands and the incidence of Cu-N and Cu-S and 454-425 and 315-250 cm^{-1} stretching vibrations in that order, in the far-IR area in 1978 [38]. The antitumor agent 3-ethoxy-2-oxo-butyraldehyde copper(II) bonding parameters to be similar bis(thiosemicarbazido) copper(II) sulfate. It may be regarded as basically liberated of Cu-S and Cu-N bonds. Thiosemicarbazone copper(II) complexes prevents malevolent makeover by Rous sarcoma virus and it has been recognized that reserve of RNA-directed DNA-polymerase in the viron by W.C. Kaska *et al.* in 1978 [39]. B.P. Mohapatra *et al*. reported the octahedral complexes, have been resultant as of ligands such as benzoin thiosemicarbazone [40], 9, 10-phenanthraquinone [41], ethylacetoacetatethiosemi carbazone in 1983 [42]. Its complex of sort $[CuLX(solv.)_n]$, wherever X is Cl, L is the ligand monoanion; solvent is DMF or H_2O ; and n = 0, 1, or 2.

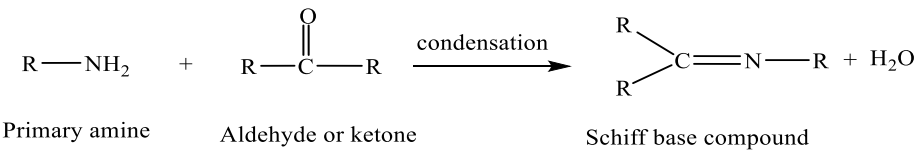
D.X. West have been reported many thiosemicarbazone moieties, involving higher denticity in addition to mono-dentate coordination in 1984 [43]. Douglas *et al*. have come into view the rock crystal of 3-hydroxy-5-hydroxymethyl-4-formyl-2-picolinethiosemi carbazone(HPictsc) [44]. This ligand coordinated with copper(I1) to form $[Cu(Pictsc)\text{-}H_2O]Cl.H_2O$ [45] was reported in 1986. The copper(II) focus has the thiosemicarbazone this olive compact deprotonated Pictsc (from ^2N) coordinated through the axomethine nitrogen, thiol sulfur and pyridoxyl oxygen by an aqua ligand finishing an almost planar arrangement. The thiosemicarbazone moiety reliant on the way of complex preparation [46-47]. E.K. John *et al*. investigation of this ^4N-dimethyl-, ^4N-ethyl- and unsubstituted thiosemi carbazone, which is radiopharmaceutical for valuation of local blood tide in the heart kidneys, and brain in 1990 [48]. Ainscough *et al.* an additional Cu(II) complex of 2-formylpyridinethiosemicarbazone derived as of the trifluoroacetate salts in 1993 [49].

Silver Complexes with thiosemicarbazone Schiff base compound

Silver salt have been used since primitive age up to the early 20th period as cures for warts and itchiness. Then in the period of 1880s, $AgNO_3$ solution have been used as eye drops for blindness. Silver therapeutic agents as an anti-inflammatory, antiseptic, and antibacterial causes are well known. Silver complexes synthesis and their action are reported widely [50-51]. Casas *et al*. has reported that thiosemicarbazones (N, S donor ligands) have extensive biological uses owing to the flexibility of presenter atoms, configurational tractability and π-delocalization. These thiosemicarbazone have significant consideration over earlier decades in 2000 [52]. Hexanuclear silver(I) complex, $[Ag_6(Hstsc)_6]$, (salicylaldehydethiosemicarbazone anion is Hstsc) which is first structure where thio-ligand organizes by $\mu_3\text{-}N^2$ was reported by Ashfield *et al*. reported in 2004 [53]. Silver(I) complexes with thiosemicarbazone has been reported more than 20 years ago but come to the view in 2004 by Ashfield *et al*. [54]. Lobana *et al*. in 2008 reported silver(I) salts (e.g: chloride, bromide, nitrate, acetate) with thiosemicarbazones(Htsc) [55-61]. In recent years, some polynuclear Ag complexes have been reported by Castineriras *et al*. in 2009 [62-63].

Gold Complexes with thiosemicarbazone Schiff base compound

Gold was the first metal which was used for treatment against rheumatoid arthritis but its exploitations in modern medicine is restricted from the mid-1930s. An Au(I) thiolate-triethylphosphine complexes was introduced as treatment agents for various diseases in 1985. Gold complexes came on the spotlight because of novel metal-based drug treatment for cancers. Recently, several reviews on gold complexes have been reported with regard to different bioactivities such as anticancer bioactivity, anticancer drug resistance, immune response, tumor cell metabolism, and anticancer mechanisms [64-68]. Thiosemicarbazones have been effectively used to form functionalized Gold (I) and Copper (I) clusters in 2006 by Zhao *et al*. [69]. Smith *et al*. reported in 2010 that free ligand compared to complexes of thiosemicarbazone enhance the antiplasmodial activity [70]. J Rust *et al*. reported in 2011 that the mixed ligands of thiosemicarbazone along with phosphine ligand of gold complex [71].



Scheme-1: The reaction between aldehyde or ketone and primary amine to form Schiff base.

Complexes of Coinage Metals

Covalency parameters and ESR spectrum of the antitumor manager 3-ethoxy-2-oxo-butyraldehyde thiosemicarbazone copper(II) was reported by Campbell *et al.* in 1976 [72]. These kinds of complexes (Fig-1) have showed mutually monomers and dimers structure. These complexes are used sulfur linking in the axial direction of two planar Cu(II) hubs to form a dimer Centrosymmetric.

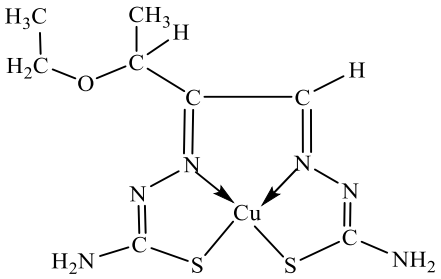
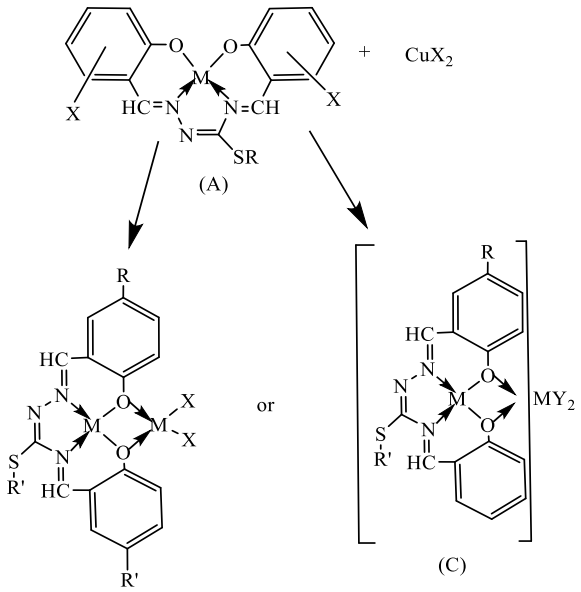


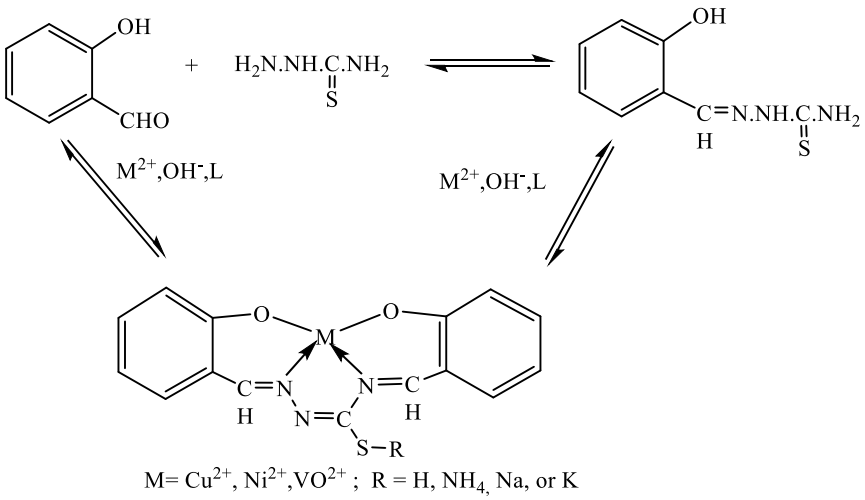
Fig. 1: Thiosemicarbazone3-ethoxy-2-oxo-butyr aldehyde copper(II) complex.

Super complexes simply as several different binuclear and trinuclear copper(II) complexes (Scheme 2) with quadridentate ligands with Cu(II), which is derived from o-hydroxybenzaldehyde and its thiosemicarbazones (A) was reported by Zelentsov *et al*. in 1977 [73]. The Super-complexes rest on upon the nature of the reactants and the anions. Similarly, bromides and chlorides donated binuclear adducts (B) of the kind $[ML.M'X_2]$, even though nitrate salts and perchlorate offered trinuclear compounds (C) of the kind $[(ML)_2M]Y_2$ (where Y = NO_3 or ClO_4), in which the nitrate ions and perchlorate stay extant as able ions in the crystal matrix but metal atom are not coordinated.



Scheme-2: Super complexes form, by the interaction of copper(II) salts with quadridentate ligands.

Gerbeleu *et al.* reported in 1982 complexes of TSCs, where sulfur atom of the ligand did not chelate with metal ions (Scheme 3) [74].



Scheme -3: Template reaction of TSCs synthesis and complexes formation without sulfur bonding [75].

A.G. Bingham *et al*. and C.F. Bell *et al.* both were reported the dimeric Cu(II) complex derived from Cu(II) acetate and 2-formylpyridinethiosemicarbazone (HFoPytsc). The tridentate N-N-S deprotonated thiosemicarbazone ligand the quarter basal site affianced by an intensely coordinated acetate oxygen (i. e. Cu-O, 195 pm). When deferred in concentrated sulfuric acid, the acetate dimer yields 2nd dimeric product in 1987 [76]. Fig-2 show that this complex Centro symmetric dimer and more weakly coordinate in bridge, axial acetate oxygen (i. e. Cu-O, 242 pm).

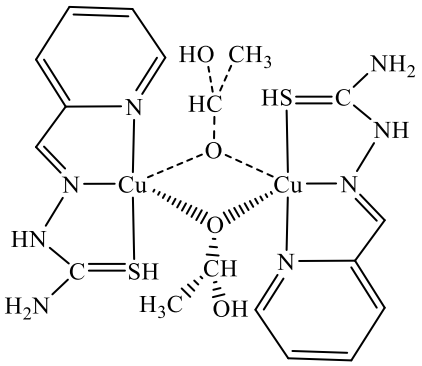


Fig. 2: Dimeric Complex of Copper[{Cu(HFoPytsc)CH_3CO_2}$_2$].

M.B. Ferrari *et al*. reported in 1989 Copper(II) complexes such as rock assemblies of the methyl ester of pyruvic acid thiosemicarbazone, HMePyrutsc, and later the ethyl ester, HEtPyrutsc [77]. This dimeric complex (Fig.3) has made bridging via chloro ligand occupying apical positions and five coordinate square pyramidal Cu(II) complex.

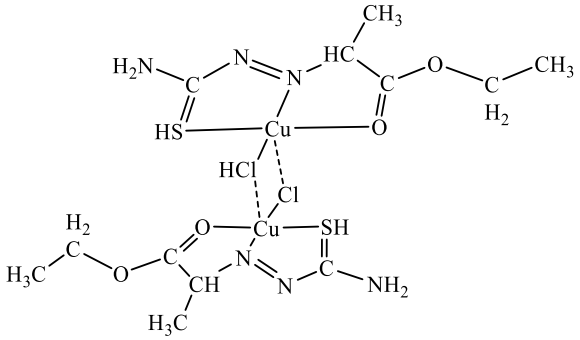
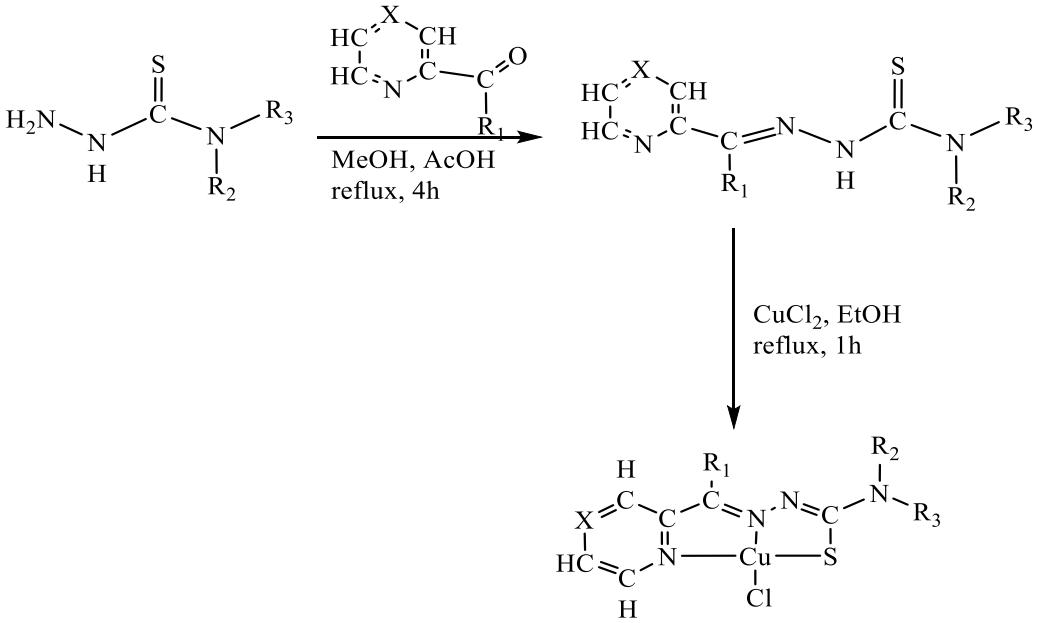
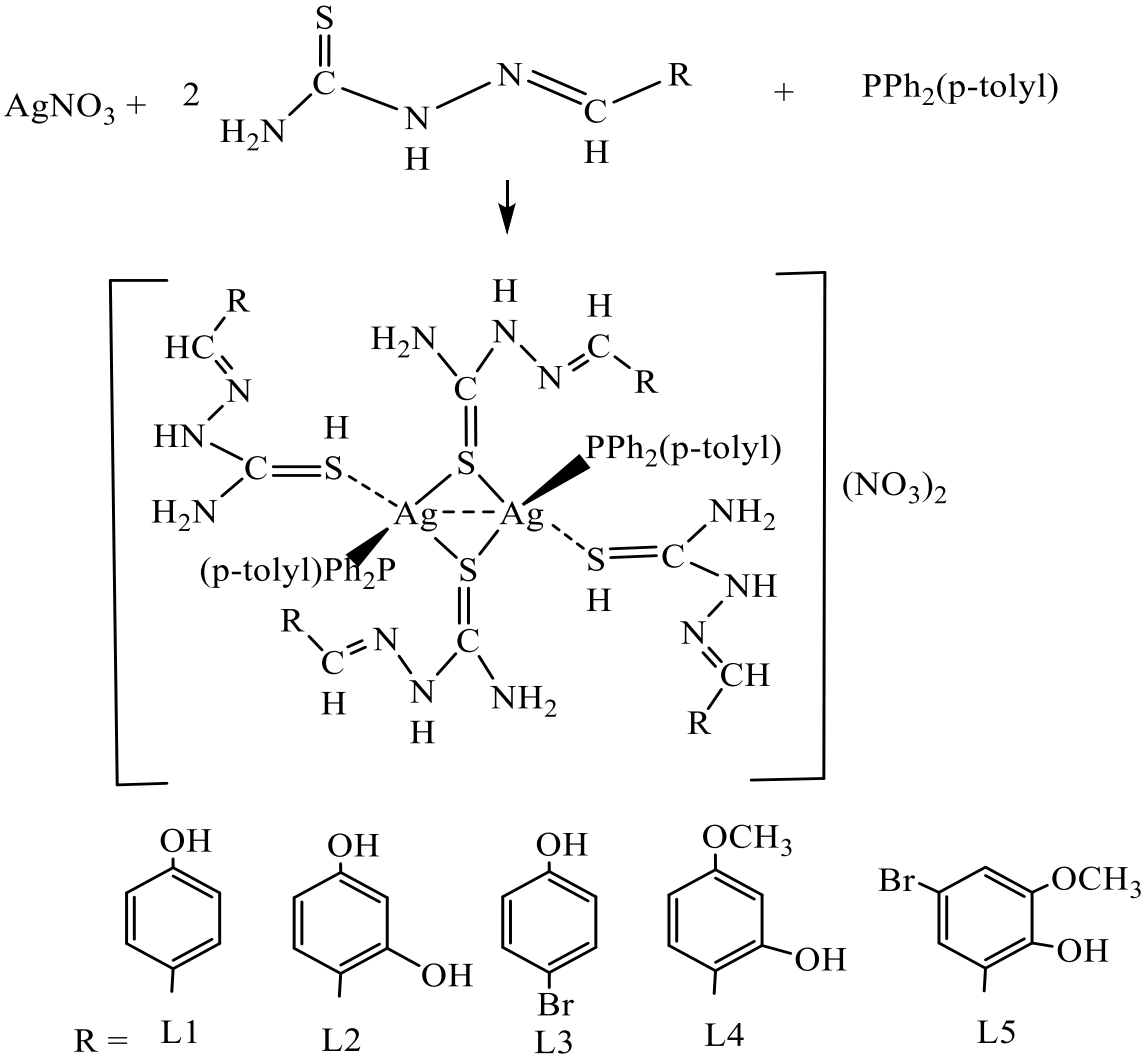


Fig. 3: [{Copper (Ethyl ester of pyruvic acid thiosemicarbazone)Cl}$_2$].

A chain of αheterocyclic-N^4 take the place of TSCs was produced through condensation method from ketone or aldehyde and their parent thiosemicarbazone. Thiosemicarbazone ligand and $CuCl_2$ with reflux to form Cu(TSC)Cl complexes (Scheme 4) was reported in1998 [78-81]. E. Shahsavani *et al*. reported few complexes of silver(I) thiosemicarbazone of varied ligands and their antibacterial properties in 2015. The Ag(I) atom be there coordinated to the Phosphorus atom of diphenyl (p-tolyl) phosphine and sulfur atom of thiosemicarbazone coordinated to Ag(I) (Scheme 5) [82- 83**]**.



Scheme -4: Common synthetic path of the thiosemicarbazones and copper thiosemicarbazone chloride complexes

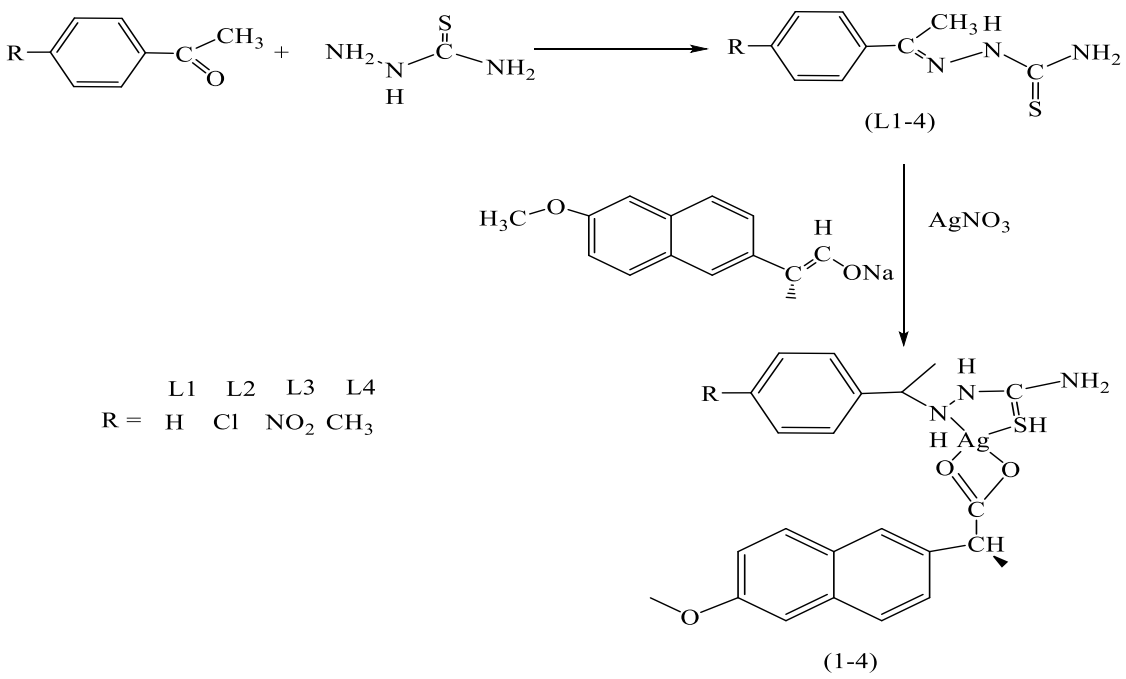


Scheme-5: Synthetic path for mixed-ligands silver complexes.

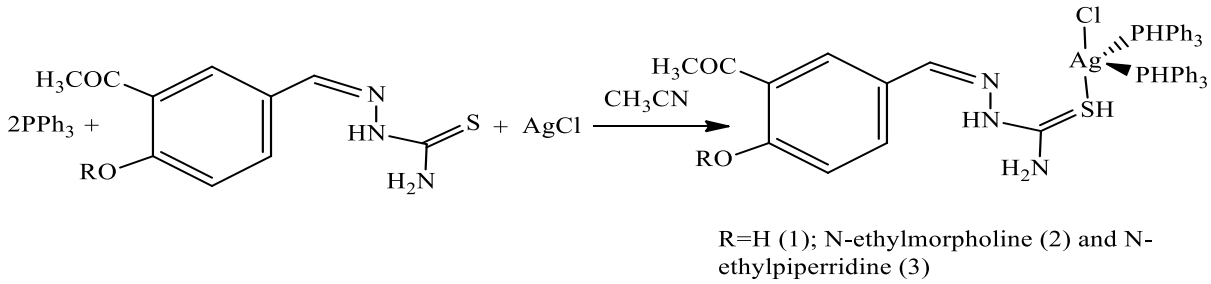
Mahendiran *et al*. reported the heteroleptic Ag(I) and Cu(II) complexes with naproxen and terpyridines. The heteroleptic Ag(I) complexes TSCs and naproxen was reported in 2015 [84-85]. The scheme-6 shows the aerobic reaction of sodium naproxen through 2-{1-(4-substitued phenyl) ethylidene)hydrazinecarbothioamide (L^{1-4}) in the presence of $AgNO_3$ in methanol to form heteroleptic Silver(I) complexes of form [Ag (L^{1-4}) (nap)].

Recently, Tavone *et al*. have adjusted polar groups of thiosemicarbazones, such as *N*-ethylmor pholine, pointing the variation of the hydrophobicity of metal complexes. They have used *N*-ethylmorpholine and *N*-ethylpiperidine with vanillin thiosemicarbazones (3-methoxy-4-hydroxybenzal dehydethiosemicarbazone) O-alkylated moieties toward develop the solubility of Ag complexes in 2018 [86]. The complexes (scheme-7) were synthesized from the reaction of the reactants, thiosemicarbazone of 3-methoxy-4-R-benzaldehyde with AgCl and PPh_3 in a molar 1:1:2 ratio.

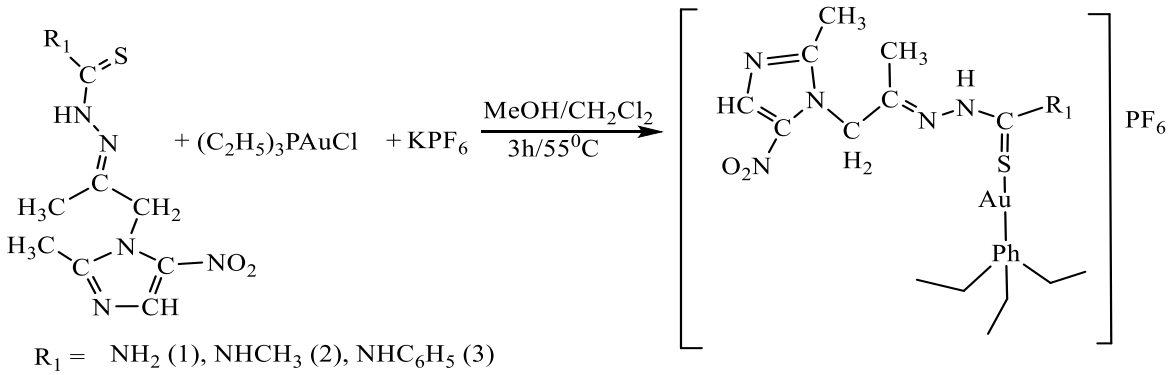
Less *et al*. reported in 2011 that Au(I) complexes through thiosemicarbazones are vastly cytotoxic, whereas constraining thioredoxin reductase (TrxR) action against mortal tumor cell. [87-88]. Triethylphosphine gold(I) complexes were gotten with secnidazole-derived thiosemicarbazones and their cytotoxic actions against normal cell and solid tumor in hypoxia and normoxia conditions were assessed in comparison with Tirapazamine.



Scheme-6: The Scheme shows formation of heteroleptic Ag(I) complexes.



Scheme-7: Reaction scheme of Silver (I) compounds.



Scheme-8: Synthesis of trietylphosphine gold(I) complexes through secnidazole-derived thiosemicarbazones (1)$[Au(HL_1)P(CH_2CH_3)_3]PF_6$, (2)$[Au(HL_2)P(CH_2CH_3)_3]PF_6$, (3)$[Au(HL_3)P(CH_2CH_3)_3]PF_6$.

The fig-4 shows one chloride ion and one anionic thiosemicarbazone ligand are attached to Au(III) center, and counter ion turns as a chloride. Gold(III) complex extremely cytotoxic against THP-1

(mortal monocytic leukemia) and HL-60 (mortal promyelocytic leukemia) cells [89].

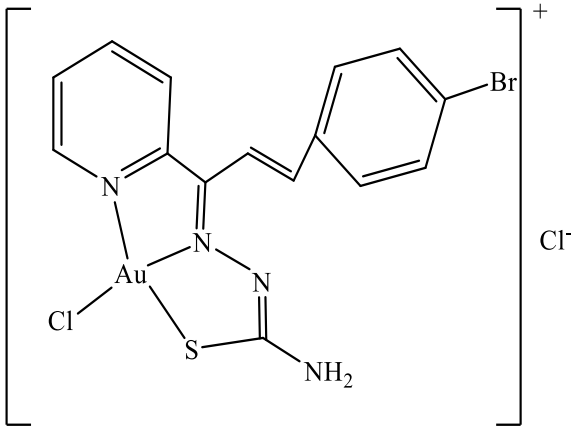


Fig. 4: Complex of [(3-(4-bromophenyl)-1-pyridin-2-ylprop-2-en-1-en-onethiosemicarba zonato)chloro gold(III)] chloride.

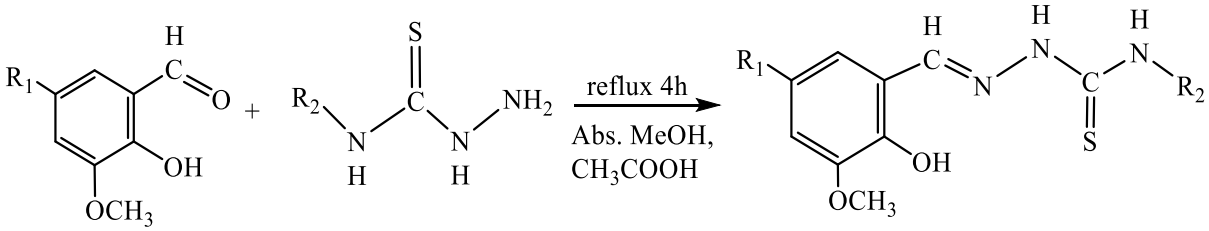
Synthesis

Synthesis of ligand

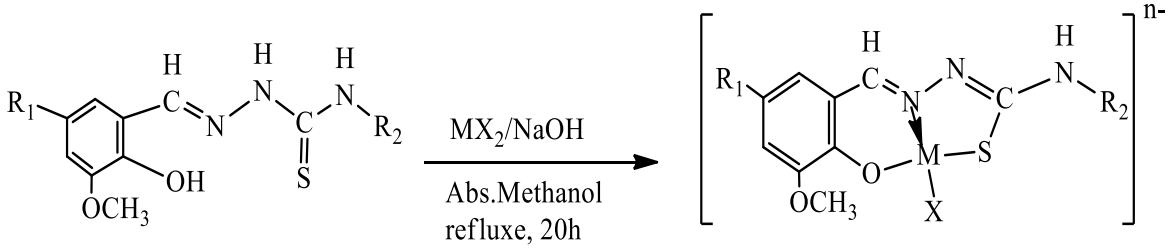
The aldehyde will be liquefied in required amount of organic solvent and acetic acid was added as catalyst (Scheme 8) [90-91]. The equivalent amine was dissolved in suitable organic solvent then will be added to the aldehyde solution. The resultant solution will be refluxed for 4 h, in a round bottomed flask with constant magnetic stirrer. The product was dried under reduced pressure then the crude product was washed with suitable solvent. The product was recrystallized with solvent evaporation technique.

Complex synthesis

The metal complexes was produced by the reaction between the NSO coordinating sites containing TSCs Schiff base ligands and the metal ions, i.e. Cu (II) Au (III) and Ag (I). The ligand and metal ion ratio in the complexes synthesis reaction was mostly 1:1 and in a few cases was 2:1 ratio [92-93]. The subsequent solution was refluxed for 20-24 hour, in a round bottomed flask with stirring. The reaction was conducted in THF, methanol, ethyl acetate or DMSO as solvent in alkaline medium. The complexes was purified by recrystallization with slow vaporization of solvent and diffusion techniques.



Scheme-9: The scheme shows the reaction between *N*-substituted carbothioamide and benzaldehyde products (OCH_3) to synthesis of Schiff base ligands.



Scheme-10: The scheme displays the reaction between tri-dentate NSO Schiff base ligands and chloride salt of metals ion in alkaline medium.

Cancer activity of thiosemicarbazone and coinage metal complexes

Copper, silver and gold are three coinage metal of group VIB of the periodic table. In the ancient world, copper, silver and gold were the coinage metals and most medieval coins. Thiosemicarbazone and their coinage metal complexes have nonlinear optical properties and various biological properties [94-98].

Anti-cancer activities of copper complexes with thiosemicarbazone Schiff base

Cancer is a fatal disease. Almost of 50 % men and 30 % women are diagnosed by cancer globally [99]. It is familiar that one-quarter of grown-ups' humanity is owing to cancer [100]. Saryan *et al.* in 1979 investigated the antitumor action of Copper (II) complex and found that are potent antitumor agents [101]. Crim *et al.* and co-workers showed that the antitumor action of 3-ethoxy-2-oxobutyraldehyde bis(thiosemicarbazone), H_2KTS, be there the four-coordinate chelate, [Copper(KTS)] [102]. M. Ligo *et al*. reported in 1977 that copper complexes of 2-acetylpyridine thiosemicarbazones have solid antineoplastic action against a number of natural murine tumors, transplantable tumors [103]. Their antitumor action is measured to include each reserve the enzyme, ribonucleotide reductase, a mandatory enzyme Deoxyribonucleic acid production in 1976 [104-105]. Antholine *et al.* studied the cytotoxicity of copper complexes of 2-formylpyridine thiosemicarbazones beside Ehrlich ascites cancer cells in 1976 [106].

Bushnell and Tasang *et al*. were investigated the benzil-bis(thiosemicarbazone) copper(II) complex and crystal structures of 3-ethoxy-2-oxo-butyral dehydethiosemicarbazone, its copper complex (the Cu(KTS)-complex), which is some related the antitumor appliance at the molecular smooth in 1979 [107]. L.A. Saryan *et al.* have been described required of the anticancer agent Cu(FoPytsc), copper(II) complex of 2-formylpyridine thiosemicarbazonato with Ehrlich ascites cancer cells in 1981 [108]. Ferrari *et al.* informed in 1998 the antitumor activities of Cu(II) complexes of 5-formyluracilthiosemi carbazone on mortal leukemic cancer cell lines K562 [109]. Hall *et al.* investigated the ligands and their Cu(II), Zn(II), Cd(II), and Ni(II) complexes exhibited like action in the suspended lymphoma and suspended leukemia cell shapes. In the mortal compact cancers their metal complexes less an inactive than the free bis(thiosemicarbazones) in 2000 [110]. Garcia-Tojal *et al*. reported the redox activities and interface of [Copper$(L)_2$] (L=thiophene-2-carbaldehydethiosemi carbazone) [111] and of [Cu(L)(NO_3)], (L= PT) and [Fe$(L)_2$]NO_3.0.5 H_2O with reduced 2-mercaptoethanol and glutathione, composed with their antitumoral and cytotoxic activity, and suggested that contact with cellular thiols, connected to the cytotoxicity of these complexes contrary to melanoma B16F10 cells and Friend erithroleukemia (FLC) in 2001 [112].

Lewis J.S. *et al*. observed in 2011 that the inhibition of topoisomerase copper(II) complexes of square planer shape. These shows cytotoxic activities and reserve of topoisomerase IIα apparently increased [113]. Despaigne *et al.* reported the TSCs containing the chalcone frame and Cu(II) complexes of these ligand These Cu(II) complexes shows potential cytotoxicity was reported in 2013 [114]. M. Jagadeesh *et al*. reported that halogen substituted TSCs, and their Cu(II) complexes are active against liver cancer [115]. The TSCs is made on the piperonal structure, exhibited potential activity against different type of colon cancer [116]. The bis(thiosemicarbazone) copper complex is found [117] or while conjugated to D-proline where the L-enantiomer is not more active in 2014 [118].

Anti-cancer activities of silver complexes with TSCs Schiff base

Liberta *et al.* have reported in 1993 that thiosemicarbazone antitumor compound such as 3-aminopyridine-2-carbaldehydethiosemicarbazone (Triapine) and their metal complexes exhibit significant cytotoxicity [119]. It is indicated that an enzyme controls the topology of DNA and the cytotoxicity of thiosemicarbazone metal complexes prevent DNA topoisomerase II was reported by Easmon *et al*. in 2001 [120].

T.S. Lobana *et al*. reported the synthesis of mixed-ligands method of Ag(I) complexes and studied their anticancer properties. Some structure of Ag (I) thiosemicarbazone complexes was reported in 2003 [121-123]. Zhang *et al*. reported that silver(I) complexes of 2-formylpyridinethiosemicarbazone and 2-thiophene-*N*(4)-methylthiosemicarbazone show similar cytotoxicity as cisplatin against colon adenocarcinoma (HCT-8) and liver (SMMC-7721) cancer cell lines in 2010 [124-125]. M. poyraz *et al.* reported silver complexes, which significant toxicity to nonmalignant cells, kidney and dermal cell. These complexes of the formula [Ag(L)$(PPh_3)_2$] (L→ benzoic acids; PPh_3 → triphenylphosphine) tempted apoptosis in mortal breast adenocarcinoma (MCF-7) and leiomyosarcoma (LMS) cell lines was reported in 2011 [126]. Silver(I) complexes of naproxen, salicylic acid and aspirin show important antiproliferative activities against breast cancer was reported by Banti *et al.* in 2012 [127-129].

S. Medici reported that if triphenylphosphine (PPh_3) was used instead of 1,10-phenanthroline the antitumor activity of silver compound get improved. Such as a result of the improvement of hydrophobicity affected in PPh_3 and these complexes tend to be more insoluble in polar solvents in 2016 [130]. M. Tavone *et al.* have tuned TSCs contain glacial groups, such as

N-ethylmorpholine, monitored the variation of the hydrophobicity of metal complexes. The solubility of Ag complexes in polar solvents to enhance, if we have used vanillin thiosemicarbazones (3-methoxy-4-hydroxybenzaldehydethiosemicarbazone) O-alkylated with N-ethylpiperidine and Nethylmorpholine moieties in 2018 [131]. Oliveira *et al*. Confirmed that thiosemicarbazones and hydrazones derived from secnidazole, Ag(I), and Bi(III) complexes of 5-nitroimidazole compound, showed to be very much active against anaerobic strains and were inactive against aerobic bacteria, at little oxygen concentrations and reduction of the nitro group potency be portion of their antimicrobial way of action in 2019 [132]. Silver complexes, $[Ag(phen)(L)]NO_3$ was not only fewer poisonous used for the non-tumor breast cell link MCF-10A, but also more active than Cisplatin. The apoptotic and cytotoxic effects of these complexes $[Ag(phen)(L)NO_3$ on TNBC cell link MDA-MB-231, where phen indicate 1,10-phenantroline; L indicate 2-formylpyridine-N(4)-R-thiosemicarbazones) in 2020 [133].

Anti-cancer activities of Gold complexes with thiosemicarbazone Schiff base

Baker *et al*. first reported the anticancer properties of a pane of cationic mononuclear $[Au(NHC)_2]^+$ (NHC, *N*-Heterocyclic carbene) and dinuclear $[Au_2(bisNHC)_2]^{2+}$ complexes [134-135] Kitanovic *et al*. defined a series of [Au(NHC)Cl] complexes behavior benzimidazole ligands with TrxR inhibition activity [136]. Lok *et al*. reported that gold(I)-thiourea complex can inhibit the activity of Trxr via gold(I) coordination with the active sites of selenocysteine selenol/ cysteine thiol [137]. Bagowski *et al*. reported a series of $[Au(PPh_3)(alkynyl)]$ complexes, which were detected to inhibit glutathione reductase and TrxR activity [138]. Powis *et al*. reported thioredoxin reductase is a selenoenzyme. It is vital for redox homeostasis and antioxidant shield. TrxR is stated in numerous cancer cell lines and inactivation has been related to reserve of chamber increase. Therefore, TrxR could be measured as a capable goal for anticancer analysis in 2006 [139-140].

Casini *et al*. reported that gold(III) complex shows antitumor activity. It is isoelectronic ($5d^8$) and quadratic (isostructural) with Pt(II) in 2008 [141-143]. Several researchers reported that Au(I/III) complexes are effective inhibitors of TrxR as the cytotoxic actions of these complexes are owing toward TrxR reserve in 2009 [144-146]. Lessa *et al*. reported in 2010 that gold complex of 2-acetylpyridine moiety containing thiosemicarbazones showed cytotoxicity against glioma cells [147-148]. Castelli *et al*. observed inhibition of topoisomerase Au(III) complexes contain square planer complexes that shows cytotoxic activities and inhibition of topoisomerase IIα significantly increased in 2011 [149]. Ponader D *et al*. have shown action contrary to a kind of tumor types of Au(I) complexes in 2012 [150-152]. Rodríguez *et al*. Gold(I) and Gold(III) complexes through thiosemicarbazones and bis-(thiosemicarbazones) to action as inhibitors of the seleno-enzyme thioredoxin reductase and to show antiprolifer active activity against cancer cells in 2018 [153-154]. Yang *et al*, Diethynylfluorene derivatives of gold(I) have been reported for their anticancer activities. In this contribution, a list of diethynylfluorenes and their gold(I) complexes have been studied, and the study found that non-metallic diethynylfluorenes show lower cytotoxicity than cisplatin [155].

1. Anti-bacterial activities of copper, silver and gold Schiff base

The thiosemicarbazone and their transitional metal complexes have potential biological activity against several bacterial infectious diseases originated by multi-drug, which are used to against Gram-negative besides Gram-positive microorganisms [156]. These have been increased at alarming rate through the ecosphere [157]. TSCs mainly NSO having chelating agents showed potential activity against bacteria. It is due to their physicochemical and pharmacological properties [158-161]. D. X. West *et al*. was reported copper(I1) complexes of [Cu(HAcPyOtscpo)X] (X = Br/ Cl) expressions diffident doings beside Paecilomyces oariotii, but 2-acetylpyridine *N*- oxide thiosemicarbazones exhibited not at all growing inhibitory doings beside Aspergillus niger, still not for instance abundant as the copper(I1) complexes of the like 2-acetylpyridinethiosemi carbazone in 1991 [162]. Bindu. P *et al*. reported *N*-4-phenyl salicylaldehyde thiosemicarbazone and it's Cu(II) complexes exhibited inhibitory against human pathogenic microorganisms, Shigella dysentariae, Salmonella typhi, non-coagulase S. aureus, and Photobacterium sp. These complexes exhibited activity against plant pathogenic fungi. The complexes demonstrate higher because the chelation increase in lipophilicity [163]. Kiraz *et al*. reported the antibacterial activity of isonicotinoylhydrazones of 3-(N-methyl)isatin and 2-thiophenecarbonyl hydrazone complexes of Ni(II), Cu(II) and Zn(II). The metal complexes of 2-thiophene carbonyl hydrazone shows potent antibacterial activity to Bacillus subtilis with MIC of 3.0-25.0 μg mL^{-1}[164]. Li, Q *et al*. reported in 2000 thiosemicarbazones and vitamin K3 was synthesized and its Mn(II), Ni(II), Cu(II) and Zn(II) complexes, which a new drug based on efficacies

against bacteria. This ligand and its complexes have strong inhibitory activities against gram negative *E. coli*, Hay bacillus and gram positive [165]. Narang *et al*. reported 2001 the antibacterial action of copper(II), cobalt(II), nickel(II), cobalt(II), manganese(II) and iron(III) complexes of (7-chloro-4-(benzylidenehydrazo)quinoline and exhibited potential activity against *E. coli S. aureus* [166]. Savini *et al*. reported in 2004 antibacterial action of copper(II), cobalt(II), cadmium(II), nickel(II), and zinc(II) complexes of acetophenone-4-aminobenzoyl hydrazone and 4-hydroxyacetophenone-4-amino benzoyl hydrazine. These showed significant activity against *A. niger* and *E. coli*. [167-169].

Conclusion

Schiff base ligands can be prepared easily through a modest concentration reaction between an aldehyde or ketone and primary amine. The biological action of thiosemicarbazones metal complexes was mentioned. Copper complexes shape may be square planer, octahedral and bi-pyramidal. Few cases it was found that copper complexes more active than cisplatin against different cancer cell lines. Silver complex may be linear. Silver complex have showed promising anticancer performance. Silver therapeutic agent as an antiseptic, anti- inflammatory and antibacterial agent are recognized. Gold (I, III) complexes have treatment of malaria, leishmaniasis, and tuberculosis and HIV infection. Gold complex is isoelectronic and isostructural, it may form square planer shape and mechanisms of anti-proliferative activity are considerably different. Some Gold complexes are unstable because their ligands are easily replaced under biological conditions. The thiosemicarbazone Schiff base complexes (Cu, Ag, Au) could be promising anticancer and antibacterial agent.

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