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Medicinal Utility of Thiosemicarbazones with Special Reference to Mixed Ligand and Mixed Metal Complexes: A Review

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Abstract—Thiosemicarbazone complexes possess structural diversity and variable bonding patterns and potential biological implications and ion sensing abilities. The ability of the transition metals to acquire different geometries like octahedral, square planar and tetrahedral in different coordination environments has encouraged researchers to explore the coordination chemistry of thiosemicarbazone complexes which can also vary upon changing aldehydes and ketones, substituents attached to the carbonyl moiety, metal and its oxidation state, geometries, counter ions, presence of a solvent or additional molecules in the structures and substituents on the S or N(4)-atoms. This review aims to summarize recent developments in the synthesis and medicinal importance of thiosemicarbazone ligands and particular emphasis on their metal complexes. The mixed ligand-metal complexes have an important role to play in biological systems because a number of ligands try to combine with the same metal ions in vivo. Different ligands have different biological activities producing synergetic results and enhancing the potency of the formed complex. They also have a role to play in the storage and transport of substances, therefore the review article also covers the mixed ligand complexes of thiosemicarbazones with hetero ligands like 1,10-phenanthroline, pyridine, triphenyl phosphine etc. and their mechanistic action and medicinal benefits in recent years. The binuclear complexes of thiosemicarbazones with two different and same metal ions have also been explored here. Dinuclear complexes have been shown to possess interesting structures and in most cases, such complexes containing metal–metal bond also affects the complex's magnetic properties as well. It has been well discussed in the course of this study that metal complexes show enhanced biological activity than the free ligand or metal ion. The studies cited in the review have been sourced from publications indexed in known databases. Some of the recently explored structural alterations have been discussed in the paper and future substituted thiosemicarbazones and their complexes may emerge as multi-target inhibitors.

Keywords: thiosemicarbazones, coordination chemistry, mixed-ligand, mixed-metal bond

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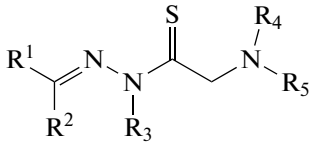
INTRODUCTION

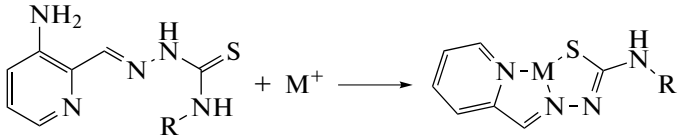
Thiosemicarbazones (TSCs) and their complexes. Thiosemicarbazones are Schiff based ligands of great biological importance. They have been under consideration for a great amount of time because of their substantial biological relevance. Since the beginning of the 20th century, the medical applications of thiosemicarbazones have been known. In the 1950s their action against tuberculosis and leprosy was being reported [1]. The antiviral properties of thiosemicarbazones led to the marketing of methisazone, (Marboran®), for the treatment of smallpox [2]. During the same time, their antitumour activity was reported for the first time [3]. Triapine® (3-aminopyridine-2-carboxaldehyde thiosemicarbazone) was also developed at the same time as an anticancer agent reaching upto phase II trials on many cancer cell lines [4, 5]. TSCs have received considerable attention because of their binding ability with metal ions and for their antitumour, antiprotozoal, antibacterial or antiviral activities [2]. Anticarcinogenic, antibacterial, anti-HIV, fungicidal, antiviral, antifungal and antitumour properties etc. have been reported involving transition metal ions with thiosemicarbazones N, S and N, O containing ligands and their complexes have been explored in great detail for their synthetic and structural features. The biological action is attributed to the multidentate chelate forming tendency with essential heavy metal ions coordinating through NNS, or ONS atoms. The probable mechanistic action involves modification in lipophilicity regulating the entry into the cell, which is altered upon coordination of metal ions. Some side effects may also be removed on complexation and the coordination complex can be more active than the uncoordinated ligand. TSCs can exist in two structural isomers (E or Z) and coordinate with the metal ion as neutral or in deprotonated form

through N and S atoms [6]. Brockman and co-workers reported the anti-leukemic effect of 2-formyl pyridine in 1956 [7]. French et al. predicted the mode of action of the α(N)-heterocyclic thiosemicarbazones having a tridentate nature, making them efficient chelators [8]. The activity enhancement was done by doing modifications to the aromatic moiety. Upon the same principle, they predicted the action of pyrazine carboxaldehyde and 1-formylisoquinoline thiosemicarbazones. Upon coordination, the thiosemicarbazone part gets hidden and the resultant metal complex exposes the hydrophobic moiety to the solvent making it feasible to cross the cell membrane. Inside the cell, the thiosemicarbazones interact with some essential enzymes which are vital to cells leading to their disruption.

Thiosemicarbazone complexes possess structural diversity and variable bonding patterns and potential biological relevance and ion sensing power [9]. The ability of the transition metals to acquire different geometries like octahedral, square planar and tetrahedral in different coordination environments has encouraged researchers to explore the coordination chemistry of thiosemicarbazone complexes which can also vary upon changing aldehydes and ketones, substituents attached to the carbonyl moiety, metal and its oxidation state, geometries, counter ions, presence of a solvent or added molecules and substituents on the S or N(4)-atoms [10]. They are highly delocalized systems, particularly when attached to the azomethine carbon. General structure of thiosemicarbazone are listed in Scheme 1, where the R^1 and R^2 groups may bear nucleophilic groups and atoms and R^3 and R^4 are the N(4) substituents. Their physicochemical properties were the main driving force to explore the coordination chemistry of thiosemicarbazones [11]. The coordination of thiosemicarbazones with metal ion is given as Scheme 2.



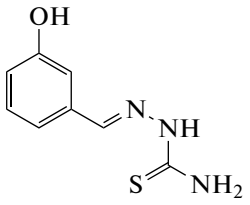
Scheme 1.



Scheme 2.

Bonding in metal thiosemicarbazone complex. In the solution state TSCs may exist in an equilibrium mixture of thione and thiol tautomers. In thione tautomeric form the ligand acts in a neutral and bidentate manner and the removal of the proton from thiol produces a single negative charge on the bidentate ligand. Based on the reaction conditions, specifically the pH, the complexing unit can be cationic, anionic or neutral. Mostly in metal complexes, the ligand is involved in an uncharged form. However, in cobalt complexes with 2-hydroxyl-1,4-naphthoquinone-1-thiosemicarbazone [H_2NQTSC] viz. [Co(HNQTSC)-(NQTSC)] HNQTSC = the mono anionic thione form, and NQTSC = the dianionic thiol form appear to contain both ligand tautomers. The behaviour can be explained based on the central metal ion and the change in oxidation state [12]. Conformational changes occur due to the nature of ligand as it can exist in protonated, deprotonated or isomeric forms. As determined by the crystal structure of thiosemicarbazide hydrochloride, the conformational changes can be explained based on protonation, deprotonation and steric hindrance. In most of the thiosemicarbazone complexes, the metal ion coordinates with the ligand in the cis-configuration [13]. In cis-form TSCs coordinate via the thione/thiol sulphur atom and azomethine nitrogen in a bidentate fashion. In presence of an additional coordinating group, the ligand acts as a tridentate species. The alkylation of the thiocarbonyl sulphur in the derivatives causes complexation from the terminal amino group also leading to acidic character [14]. While complexation with Cu(II), Ni(II), VO(IV), the ligand condensed at the last amino group through another carbonyl compound to act in a quadridentate manner. The properties of the thiosemicarbazones alter with the modifications in their chelating power and the binding patterns to the metal atom [15]. Under certain experimental conditions, carbonyl thiosemicarbazones also undergo cyclization. Usually, the ligands coordinate through sulphur, azomethine nitrogen and other heteroatoms present in the structure [16] and also to the metal they are coordinating with. The geometry of the resulting complex also depends upon the donor atoms and subsequently impacts the biological properties of the compound [17].

Stereochemistry and oxidation states. According to the hard soft acid-base (HSAB) concept given by Pearson in the early 1960s, the oxidation state of the metal has a very important role in determining its hard or soft character. The softness of a metal ion increases as the positive oxidation state decreases. Low spin d^8 ions like Pd and Pt in +2 oxidation state, and Au in +3 oxidation state and d^{10} ions like Cu, Ag, and Au in +1 oxidation state and Hg in +2 oxidation state have higher stability constants when they coordinate with S containing ligands owing to the strong sigma and d_π–d_π bonds formed by the donation of electron pair to the ligand [18]. The stereochemistry of the thiosemicarbazone-metal complexes is also altered by the presence of an additional coordinating atom or group present in the ligand and charge over the ligand. Benzaldehyde thiosemicarbazone usually acts as a neutral bidentate ligand and gives complex of the type $[ML_2X_2]$, where M = Co(II), Ni(II), Cu(II) or Fe(II), L = thiosemicarbazone ligand and X = monoanioninc ligand. The reaction depends upon the pH of the reaction medium. Salicyldehyde thiosemicarbazone (Scheme 3) on the other hand acts as a tridentate uni negative ligand forming complex of the type ML_2 which may be low or high spin.



Scheme 3.

The most common stereochemistries assigned to the thiosemicarbazone complexes are octahedral or square planar. Some five-coordinate structures of Co(II), Fe(II) and Ni(II) complexes with acetone thiosemicarbazones [19] and Fe(III) complex of 2-acetylpyridine thiosemicarbazone have also been observed [20]. Trivalent metal ions (M = Co, Fe, Re) form a complex of the type $[ML_2]^+$ which is readily synthesized by in basic medium [21]. In the case of only one reacting ligand molecule, a complex of the type $[MLX_2]$ (M = Ir) has been isolated, where X may be halides or acetate. $[ML_2]^{2+}$ type complexes with divalent metal ions and tridentate thiosemicarbazones have been prepared in the molar ratio of 1 : 2 as in the case of Mn. $[ML_2]$ and [MLX] type complexes have also been synthesized with tridentate ligands [22, 23]. The redox properties of the complex when the free ligand binds with the metal ion present in the cellular environment is an important parameter. Through cyclic voltammetry studies, the redox chemistry of Ga and Fe complexes has been explained, where L is an N-heterocyclic functionalized thiosemicarbazone [24]. Two reduction waves were obtained in non-aqueous solution in the range −1.12 to −1.49 V and −0.74 to −1.30 V. These values moved to positive side in water and to be irreversible. Fe complex showed supplementary reduction waves.

BIOLOGICAL ACTIVITY OF THIOSEMICARBAZONE COMPLEXES

Anticancer properties. Cancer is caused due to uncontrolled growth of cells showing malignant behaviour [25]. The disease without a doubt is one of the major health concerns in our society and the main focus of medicinal chemistry research. It is caused by genetic mutations and by environmental factors [26]. The drugs act differently depending on their respective concentrations with different mechanisms. The effect of the induced drug varies on normal and neoplastic cells. In most cases, it hinders mitosis or cell division in rapidly dividing cells. Tumours with high growth rates are more sensitive to chemotherapy, whereas cells with slow growth rates show a delay in response [27]. The anticancer drugs may act through the following mechanisms:

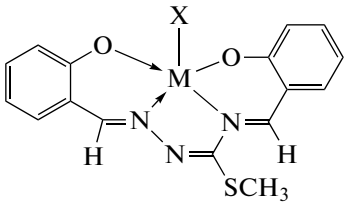
(1) causing damage to the DNA of the affected cancer calls;

(2) by inhibiting the formation of new DNA to stop cell replication, to stop tumour growth;

(3) by inhibiting mitosis of the parent cells into new cells.

Coordination to metal ions enhances the activity of the thiosemicarbazone moiety manifolds because of the diverse coordination geometries that enable the synthesis of compounds with unique stereochemistry as compared to pure organic ligands [28].

Many TSC complexes have been used as anticancer agents. Mostly the activity has been found to depend upon the typology of tumour cells. The cytotoxic activity is not only dependent on the presence of metal ions but also on the position of the substituent on the ring. Complexes of Fe(III) and Ni(II) with S-methylthiosemicarbazone of 2-hydroxy-R-benzaldehyde showed maximum activity when the methoxy ($-OCH_3$) group was attached to the side chain aromatic ring. The complexes were tested against chronic myeloid leukaemia (K562) and human endothelial (ECV304) cell lines by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The Fe substituted chelates showed maximum cytotoxic activity against K562 while those with Ni showed accelerated activity against ECV304 and K562 [29] (Scheme 4).



M = Fe/Ni
X = Cl

Scheme 4.

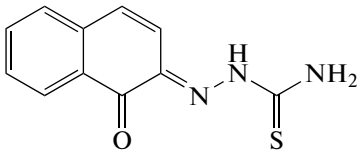
Several studies have been published on the modifications in structures of aldehydes and ketonic carbons, and the coordination positions of thione group and positions of pyridine/isoquinoline moiety in α-N heterocyclic TSCs. The N(4) substituted thiosemicarbazones have shown enhanced activity against various cancer cell lines. Though due to poor water solubility, the effect on in vivo systems is quite low and hence they need some structural modifications. The Cu(II) complexes prepared from N(4) substituted thiosemicarbazones $[Cu(p\text{-Clbhtsc})_2]Cl_2{\cdot}2H_2O$, $[Cu(p\text{-Mbhtsc})_2]Cl_2{\cdot}2H_2O$ and $[Cu(p\text{-Nbhtsc})_2]Cl_2{\cdot}2H_2O$, where (*p*-Clbhtsc) = *para*-chloro benzaldehyde thiosemicarbazone, (*p*-Mbhhtsc) = *para*-methoxy benzaldehyde thiosemicarbazone, (*p*-Nbhtsc) = *para*-nitro benzaldehyde thiosemicarbazone have been tested against MCF-7 showing the first complex to have highest cytotoxicity [30]. The Co(III) complexes with pyridoxal N(4)-substituted thiosemicarbazone ligands are obtained from $[CoCl_2(PPh_3)_2]$ and pyridoxal-*N*-methyl-thiosemicarbazone hydrochloride/ pyridoxal *N*-phenyl-thiosemicarbazone. Substitution from methyl (Me) or phenyl (Ph) groups on terminal N(4) nitrogen has increased the potential binding and cleavage of DNA, free radical scavenging and cytotoxicity [31]. Detailed studies are still required to understand the mechanism at the cellular level and to better understand the role of metal ions. Neutral and ionic copper bis(thiosemicarbazone) complexes with methyl, phenyl, and hydrogen as substituents have been tested in vitro. Bis copper chelates derived from glyoxal bis(4-methyl-4-phenyl-3-thiosemicarbazone) showed potential activity against human cancer cell lines. Tritiated thymidine incorporation assay showed that the chelates also inhibited DNA synthesis considerably. Cu(GTSC) and Cu(GTSCHCl) induce apoptosis in HCT116 and caused DNA cleavage and topoisomerase IIα inhibition. In vivo dosing of Cu (GTSC) inhibited tumour progression in HCT116 xenografts in nude mice [32]. Novel phytochemicals, quercetin thiosemicarbazone Cu(II) complex, quercetin 3-O-glucoside thiosemicarbazone and its rutin derivative possessed tetrahedral and octahedral (rutin) structures and antitumour and anticancer activities. In an extended study by the same authors, Schiff bases of certain constituents, viz. flavanoids/phytochemicals and transition metal complexes with Pt, Au, Pd, Ru, Co, Fe, Ni, Zn and Cr have been found to be excellent candidates for the development of novel anticancer drugs [33]. Anticancer properties of 6-hydroxy chromone-3-carbaldehyde thiosemicarbazone and its Ni(II) complex were investigated *in vitro* against different cancer cell lines, where Ni(II) complex has shown to exhibit significant cytotoxic activity. The interactions of Ni(II) complex and ligand with CT-DNA have been analyzed by spectrometric titrations. The Ni(II) complex interacted with DNA by intercalative mode. The intrinsic binding constants of Ni(II) complex and ligand with DNA were in the range of $1.10 \pm 0.65 \times 10^6$ M^{-1} to $1.48 \pm 0.57 \times 10^5$ M^{-1} [34].

Mechanisms of action responsible for the anticancer/cytotoxic activity of thiosemicarbazone complexes. Thiosemicarbazone complexes due to their considerable biological activity have raised questions about their working mechanism and the intracellular targets they bind with. Currently, the known targets related to their anticancer activity are production of reactive oxygen species [35], suppression of ribonucleotide reductase (RR) and topoisomerase II (topo II) [36], mitochondria disruption and multidrug resistance protein (MDR1) inhibition [37] as discussed below.

Inhibition of ribonucleotide reductase (RR). RR is an iron-dependent enzyme. The enzyme governs the reduction of ribose to deoxyribose through the free radical pathway. Tyrosyl radical promotes the overall activity. When the enzymatic activity is inhibited, it blocks the cell cycle, eventually leading to apoptosis and cell death. The enzyme is essential for DNA synthesis. 5-Hydroxy-2-formyl pyridine (5-HP) was one of the first thiosemicarbazone compounds to inhibit RR. The action of the compound involved tyrosyl free radical destruction [38]. Some formyl pyridyl thiosemicarbazones can also act as strong RR inhibitors. 1-Formylisoquinoline thiosemicarbazone and 2-formylpyridine thiosemicarbazone in their activity mechanism have indicated the presence of a hydrophobic pocket in the enzyme interacting with the aromatic system leading to methylation of the aromatic ring and enhanced activity [39]. Fe scavenging role of N-heterocyclic thiosemicarbazone complexes with Fe and Ga has been studied as iron chelators [39]. The Ga complex showed higher cytotoxicity but lower RR inhibition, indicating some other mode of action. Though Fe(II)bis(triapine) complex was found to be a more effective RR inhibitor generating hydroxyl radical in an aqueous medium in the presence of oxygen and quenched tyrosyl radicals present in the smaller subunit of RR [32]. The study provided evidence that complexation of Fe has an important role in reducing the availability of Fe for RR [39]. Radical generation can also initiate the Fenton type of reaction and leads to the generation of hydroxyl radicals in the presence of oxygen. ROS generation can also degrade DNA.

Inhibition of topoisomerase II. Topo I and II enzymes have the potential to control DNA topology and are essential for cell maintenance, DNA replica-

tion and chromosome organization [40]. Rapidly proliferating tumour cells have a high level of topo II making them a potent target for anticancer agents. In many cases, thiosemicarbazones have been found to inhibit the topo II enzyme. A ligand with a quinolone group has been found to have potential cytotoxicity and caused topo II inhibition. Further studies on the mechanism hinted that the enzyme-mediated ATP hydrolysis is blocked upon the binding of the ligamd to the ATPase domain of the enzyme. Antitumour activity of 1,2-naphthoquinone-2-thiosemicarbazone (Scheme 5) and its Cu, Pd and Ni complexes in +2 oxidation state have been investigated against MCF-7 cell line confirming them as effective antitumour agents known to inhibit topo II. Ni complex had the lowest IC_{50} values [41]. In a recent finding, it was concluded that α-heterocyclic thiosemicarbazones and their Cu(II) complexes catalytically inhibited topo IIα between 0.3–7.2 μM [42]. The Cu complex of acetylpyridine methylthiosemicarbazone has been shown to inhibit topo IIα. The Pt(II) and Pd(II) complexes with the same ligand showed that Pd(II) complexes had the same activity as Cu(II) complexes [43].

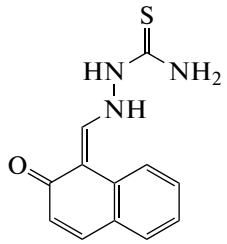


Scheme 5.

Reactive oxygen species generation. Most of the thiosemicarbazone complexes contain redox metal ions that generate O_2 and $OH^{\cdot}$ radicals. Redox metal complexes can act as ROS generators. Two Cu complexes $[Cu(L)_2(Pz)](ClO_4)]$ and $[Cu(L)_2(Dca)](ClO_4)]$ of 2-formylpyridine thiosemicarbazone with pyrazine and dicyanamide have been studied for their DNA cleavage activity. The oxidative cleavage of DNA was tested with 3-mercaptopropionic acid as a reducing agent by gel electrophoresis using supercoiled pUC18. Both complexes produced single and double-strand rupturing in DNA in the presence of 3-mercaptopropionic acid. The activity of the complexes suggested that they could act as hydroxyl radical generators [44].

Multidrug resistance protein (MDR1) inhibition. Multidrug resistance is the most important aspect and clinical challenge in drug discovery, particularly for anti-cancer drugs. In some cases tumours develop MDR making it difficult for other drugs to act upon them [45]. The Pd complexes with phenanthrene quinone thiosemicarbazone were evaluated for anti-proliferative properties against breast cancer cell line. The complex showed significant anti-neoplastic properties exclusively against the cancer cells was effective against drug-resistant breast cancer cells [46]. Recently developed thiosemicarbazones have exhetered their effect on the selected cell lines, as opposed by the P-glycoprotein (P-gp), an important MDR regulator [47, 48]. Two Schiff base derivatives including anthracene-9-carboxaldehyde thiosemicarbazone were explored for their intercalation with DNA their anti MDR properties. They exhibited antiproliferative properties against MCF-7 and DOX-resistant MCF-7/ADR cell lines with low DRI, showing that they may overcome MDR. Thiosemicarbazone and anthracene derivatives exhibited high possibility of overcoming MDR in vitro with a low DRI [49].

Antibacterial activity. Pathogenic diseases are caused by bacteria, fungi and viruses and are of huge medical importance. Pathogens associated with biofilms are very dangerous and challenging to treat. Their typical physiology and intricate structure is the important factor that contributes to their resistance to host immune response and antimicrobial drugs [50]. Pathogenic infections are usually treated with broad-spectrum antibiotics. However, they have their fair share of side effects that affect normal microbial flora and drug resistance. New antimicrobial agents are needed for an improved mode of action and the discovery of new pharmacological targets is also needed so that the application of broad-spectrum antibiotics and the emergence of antibiotic resistance must be averted. Drugs having antibacterial properties must halt the bacterial growth or kill the microorganisms without causing harm to the host. Generally they act by inhibiting the production of peptidoglycan, nucleic acid replication or causes changes in translation pattern by blocking transcription of proteins or topoisomerases [51]. Antibacterial activity of 2-acetylpyridinethiosemicarbazone complexes of Pt(II) and Pd(II) has been assessed against *S. aureus* and *E. coli* [52]. Benzilbisthiosemicarbazone and its complexes with Co and Ni in +2 oxidation state have been tested against *B. macerans* and *P. striata* with complexes being more active than the ligand [53]. Cu(II) and Ni(II) complexes with pyridinecarboxaldehyde thiosemicarbazone have been evaluated against *P. striata* and *B. macerans* showing comparable activity with the standard antibiotic streptomycin [54]. The chloroform solution of Ag(I) complex of 2-acetylpyridine thiosemicarbazone was active against a number of bacterial strains, whereas it was inactive in aqueous solution which may be due to their low solubility. Ru(II) complexes of salicaldehyde 4-phenyl thiosemicarbazone, 2-hydroxy-1-naphthaldehyde thiosemicarbazone (Scheme 6) and 2-hydroxy-1-naphthaldehyde 4-phenyl thiosemicarbazone showed high minimum inhibitory concentrations (MICs) in comparison with oxytetracyclin and kanamcin [55]. The presence of bulky groups at the N(4) position of the thiosemicarbazones may improve the activity. These activities have shown that thiosemicarbazones can act as able chelating agents against metals like Fe, Cu and Zn [56]. This property must be further explored in pharmaceutical development and formulation especially in antimicrobial drugs [57].



Scheme 6.

Antiviral activity. Isatin-β-thiosemicarbazone and its derivatives have shown activity against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). The structure-activity relationship showed that the thiourea and NH groups enhanced the activity of the compounds [58]. Thiosemicarbazone derived from retinoids has also possessed potential antiviral activity [59]. The activity was tested against the human varicella-zoster virus. In another study Pd(II) and Pt(II) complexes of 5-substituted thiophene-2-carboxaldehyde thiosemicarbazone were tested against cytomegalo virus. Pd(II) complex showed slight and selective activity against the virus [60].

Antimalarial activity. Exploration of the antimalerial activity of chimers of ferroquine and thiosemicarbazones has been done and aminoquinoline thiosemicarbazone part was responsible for the activity [61]. The Pd(II) complex of 3,4-dichloroacetophenone thiosemicarbazone along with the ligand was tested against 3D7 (chloroquine-sensitive) and K1 (chloroquine and pyrimethamine resistant) *P. falciparum* strains. The metal complex exhibited improved activity than the uncoordinated thiosemicarbazone [62].

Antitrypanosomal activity. The trypanosomes are unicellular microscopic protozoans widely spread in nature and live as parasites on insects, plants, animals etc. Drugs exhibiting anti-trypanosomal action have been found to inhibit glycosis pathway. Thiosemicarbazone derivatives based on pyridine and their complexes with Sb(III) were tested against *Trypanosoma cruzi* exhibiting greater activity as compared to benzimidazole and nifurtimox [63]. N(4)-methyl-4-nitroacetophenone and N(4)-methyl-4-nitrobenzophenone thiosemicarbazone complexes with Mn(II) were tested against *T. cruzi* in vitro [64].

Antifungal activity. Complexation or chelation leads to improved antifungal activity [65]. The high lipophilivity of the complexes may breakdon the permeability barrier of the cell. Pt(II) complex of 2-acetylpyridine thiosemicarbazone was found to be effective against yeast. Antifungal activity of dimethylsilicone(IV) complexes of heterocyclic thiosemicarbazones have been tested against different pathogenic fungi [66].

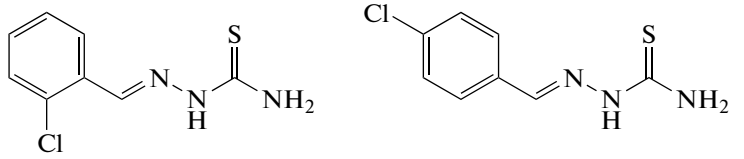
Analgesic and anti-inflammatory activity. Exposure to physical strain, chemical or microbial agents causes tissue injury which leads to a protective response in the form of inflammation. Infalmmation causes inhibition of prostaglandin at the injury site [67]. Prostaglandin E_2 (PEG2) sensitizes the nerve endings when chemical mediators like bradykinin, histamine etc. are released as inflammatory response. Thiosemicarbazone derivatives of isatin, isatin-3-*p*-chlorophenylimine have been shown to possess anti-inflammatory activity as suggested by the Carrageenan induced paw oedema method and analgesic action of the same compounds was studied by the tail-flick and hot plate method [68].

As sedative and hypnotics. Substituted thiosemicarbazides of aromatic aldehydes and acetic anhydrides have been used to prepare acylated compounds. The compounds were tested for locomotor activity. The acylated compound showed better activity than thiosemicarbazones [69].

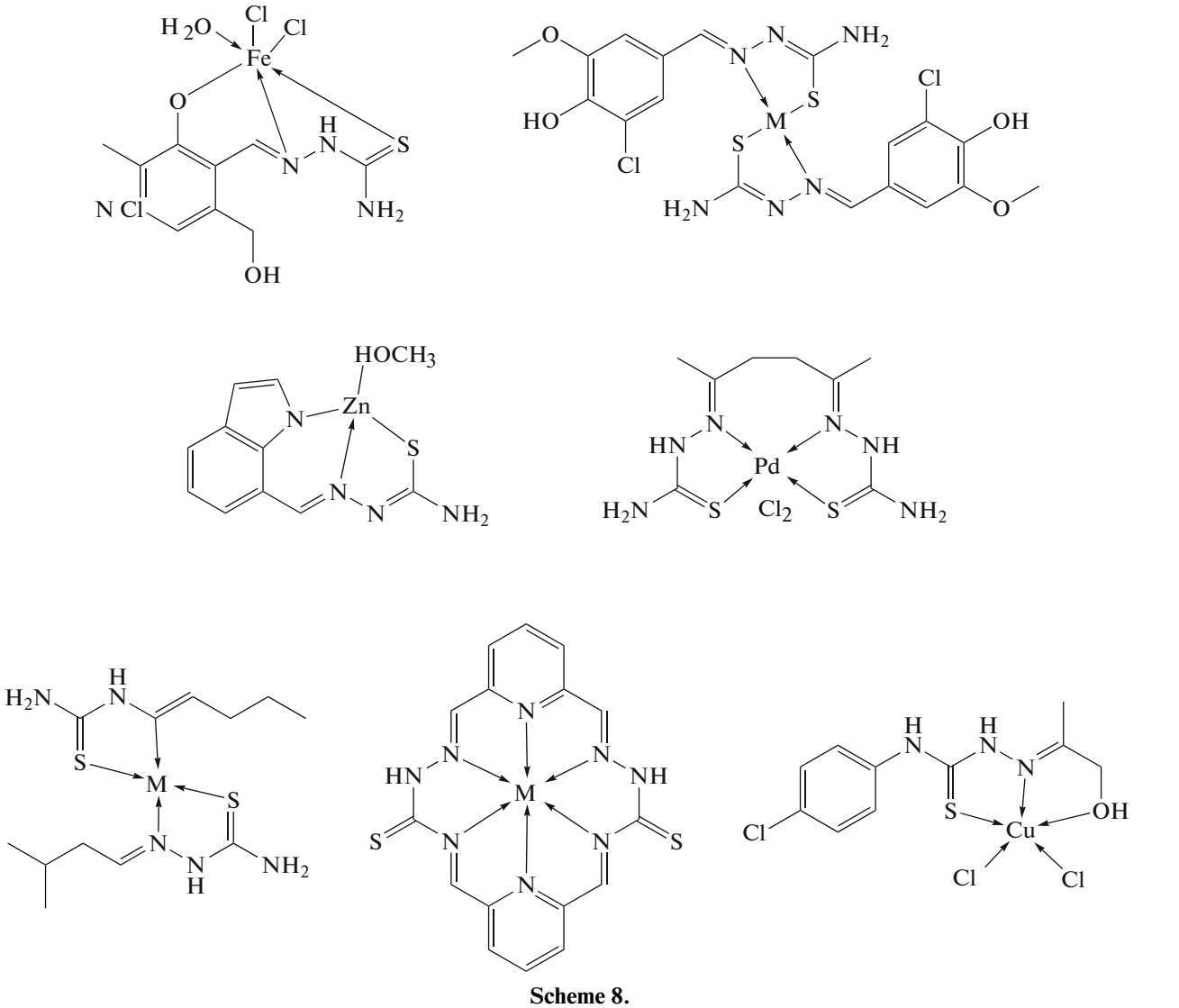
Anti-HIV activity. HIV represents an RNA retro virus which is represented by HIV-1 and HIV-2. HIV-1 is responsible for causing AIDS in humans. HIV-1 is less virulent though it causes immune suppression. 1-[*N*,*N*-dimethylaminomethyl]isatin-3-[-1'(6-chloro benzothiazol-2''-yl)] derived from 3-[-1(-6-chloro benzothiazol-2-yl) thiosemicarbazone] was tested for anti HIV activity against HIV-1 and was found to be active [70].

Inhibition of tyrosinase. Tyrosinase has an important role in melanogenesis and excessive production of melanin causes hyperpogmentation skin disorders and enzyme induced browning in plant based food items. Tyrosinase is the most common target for melanogenesis inhibition and inhibitory action of compounds against tyrosinase is not only of interest for drugs and cosmetics, but also in food and beverage industry. Thiosemicarbazones and their metal complexes have been explored for the inhibition of tyrosinase [71] which is involved in the inhibition of melanogenesis. It is also used in the formation of anti-hyperpigmentation agents. Tyrosinase contains two copper atoms and form coordination complex easily with preferred coordination with S atoms of the ligands. The thiosemicarbazones can lose a proton and thereby inhibit the activity of tyrosinase [72, 73] as benaldedyde thiosemicarbazone and its derivatives have shown [74, 75]. Presence of heterocyclic moieties also influence the inhibitory action [76]. The substitution at different positions have also altered the activity pattern. Substitution of hydroxy or methoxy groups the fourth position has greatly affected the activity of the compound [77, 78]. A series of twelve monosubstituted thiosemicarbazones were tested for their anti-tyrosinase activity. Molecular docking studies showed that the sulfur atom of the thiourea infiltrated the active site to interact with metal ion. The para substituted compounds had higher affinity for the enzyme as compared to their ortho and para substitutes [79]. Tyrosinase inhibitory activity of a series of hydroxyphenyl thiosemicarbazones was tested using kojic acid as a reference. The compounds were also tested on human fibroblasts, and were non-cytotoxic and did not activate cells in a pro-inflammatory way [80]. A series of 12 halogenated

thiosemicarbazones were tested for their inhibitory action against diphenolase of mushroom tyrosinase and their ability to inhibit melanogenesis in B16F10 murine, melanoma cell line. Melanin production was inhibited by all the synthesized compounds at the micromolar level. Some of the compounds showed IC_{50} between 0.5–0.9 μM [81]. Inhibition of 2-chlorobenzaldehyde thiosemicarbazone and 4-chlorobenzaldehyde thiosemicarbazone (Scheme 7) was studied [82] and for 2-chlorobenzaldehyde thiosemicarbazone IC_{50} was 1.54 and for 4-substituted derivative it was 6.7. Table 1 sumamrizes some recent developments in thiosemicarbazone based complexes. Some coordination modes found in mononuclear thiosemicarbazone complexes are given as Scheme 8.



Scheme 7.



Scheme 8.

Table 1. Some newly reported thiosemicarbazones

Ligand	Metal	Activity	Year	Reference
3-Chlorovanillin thiosemicarbazone	Cu(II), Zn(II), Ni(II), Co(II)	Antimicrobial	2014	[83]
4-Formylpyridine-4 N-(2-pyridyl) thiosemicarbazone	Mn(II),Fe(III), Co(II), Ni(II), Cu(II), Cd(II), Hg(II), and UO_2(II)	Antimicrobial	2014	[84]
Proline-2-formylpyridine thiosemicarbazone Hybrids	Cu(II), Zn(II), Ni(II)	Antiproliferative Activity, and hR2 RNR Inhibition	2014	[85]
Indole-7-carbaldehyde thiosemicarbazone	Zn(II), Cd(II), Pd(II) , Pt(II)	Cytotoxic and Apoptosis-Inducing Properties of the Pt(II) Complex	2014	[86]
2,6-Pyridinedicarboxaldehyde-thiosemicarbazone	Cr(III), Co(II), Ni(II), Cu(II)	Antimicrobial	2014	[87]
Ethylacetoacetate bis(thiosemicarbazone)	Cr(III), Mn(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II)	Antitumor and antimicrobial properties	2014	[88]
2,5-Hexanedione bis(thiosemicarbazone), HBTS	Fe(III), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Hg(II), Pd(II), Pt(II)	NA	2014	[89]
(1,3-Dioxoindan-2-yl)-ethylidenethiosemicarbazone (IETS)	Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Fe(III), V(III), Cr(III)	NA	2014	[90]
Polymer ligand (STFB) of salicylaldehyde and thiosemicarbazide with formaldehyde	Mn(II), Co(II), Ni(II), Cu(II), Zn(II)	Antimicrobial	2014	[91]
(E)-2-(1-(4-Hydroxyphenyl)ethylidene)-*N*-(pyridin-2-yl)hydrazinecarbothioamide (H_2PHAT)	Mn(II), Co(II), Ni(II), Cu(II), Cd(II), Hg(II), U(VI)O_2	Antibacterial, DNA degradation	2014	[92]
Pyridoxal thiosemicarbazone ligands PLTSC·HCl·2H_2O	Fe(II)	NA	2015	[93]
Pyridoxal TSC PLTSC	Cr(II)	NA	2015	[94]
(E)-4-(4-Chlorophenyl)-1-(1-hydroxypropan-2-ylidene)thiosemicarbazide	Co(III), Ni(II), Cu(II), Zn(II)	DNA binding and cleavage study *E. coli*	2015	[95]
(E)-1-(1-Hydroxypropan-2-ylidene)thiosemicarbazide	Co(III), Ni(II), Cu(II), Zn(II)	Antimicrobial	2015	[96]
1-(1-(Pyridine-2-yl)ethylidene)thiosemicarbazide (L1,) and 1-(1-(2,4-dihydroxyphenyl)ethylidene)thiosemicarbazide (L2)	Cu(II), Ni(II), Zn(II), Co(II), Mn(II), VO(IV)	Antibacterial	2015	[97]

Table 1. (Contd.)

Ligand	Metal	Activity	Year	Reference
4-Nitro-, 3-nitro-, 4-hydroxy-, and 4-amino- acetophenone thiosemicarbazone	Co(II), Ni(II)	Antibacterial	2015, 2016	[98]
l-Proline and homoproline-4-*N*-pyrrolidine-3-thiosemicarbazone hybrids	Ni(II), Pd(II), Cu(II)	Antiproliferative	2016	[99]
3-Methyl butanalthiosemicarbazone	Co(II), Ni(II), Zn(II), Cd(II), Hg(II), Cu(II), Fe(III)	Antibacterial	2016	[100]
2-Benzoylpyridine *tert*-butyl thiosemicarbazone (BZP-tBTSC), and 2-benzoylpyridine benzyl thiosemicarbazone (BZP-BzTSC)	Cu(II)	Anticancer	2016	[101]
Terepthalaldehyde-thiosemicarbazide	Cu(II), Zn(II)	Antibacterial	2016	[102]
(E)-2-((E)-2-(Hydroxyimino)-1,2-diphenylethylidene)-*N*-(pyridin-2 yl) hydrazinecarbothioamide (H_2DPPT)	Fe(II), Ni(II), Zn(II), Hg(II)	Antibacterial	2017	[103]
3-Acetyl- or 4-acetylpyridine thiosemicarbazone	Ni(II), Cu(II), Co(II)	Anticancer	2017	[104]
2-((4,9-Dimethoxy-5-Oxo-5H-Furo[3,2-g]Chromen-6-yl)Methylene) Hydrazinecarbothioamide	Cd(II), Cu(II), Zn(II), Ni(II), Co(II), VO(II), Mn(II)	Antiproliferative	2018	[105]
2-Propionylthiazole ethylthiosemicarbazone (PTZ-ETSC), and 2-propionylthiazole *tert*-butylthiosemicarbazone (PTZ-tBTSC)	Cu(II)	Anticancer	2018	[106]
2-Acetylpyrazine N(4)-phenyl-thiosemicarbazone (H2L1) 2-Acetylpyrazine N(4)-(4-chloro-phenyl)thiosemicarbazone (H_2L2)	Cu(II), Ni(II)	Antibacterial	2019	[107]
H2L1 = 4-(*p*-Methoxyphenyl) thiosemicarbazone of o-hydroxynapthaldehyde, HL2 = 4-(*p*-Methoxyphenyl)thiosemicarbazone of benzoyl pyridine and H2L3 = 4-(*p*-Chlorophenyl)thiosemicarbazone of *o*-vanillin	Zn(II)	Cytotoxic	2020	[108]
3,5-Diacetyl-1,2,4-triazole bis(4-*N*-isopropylthiosemicarbazone)	Pt(II)	Antitumoral	2020	[109]

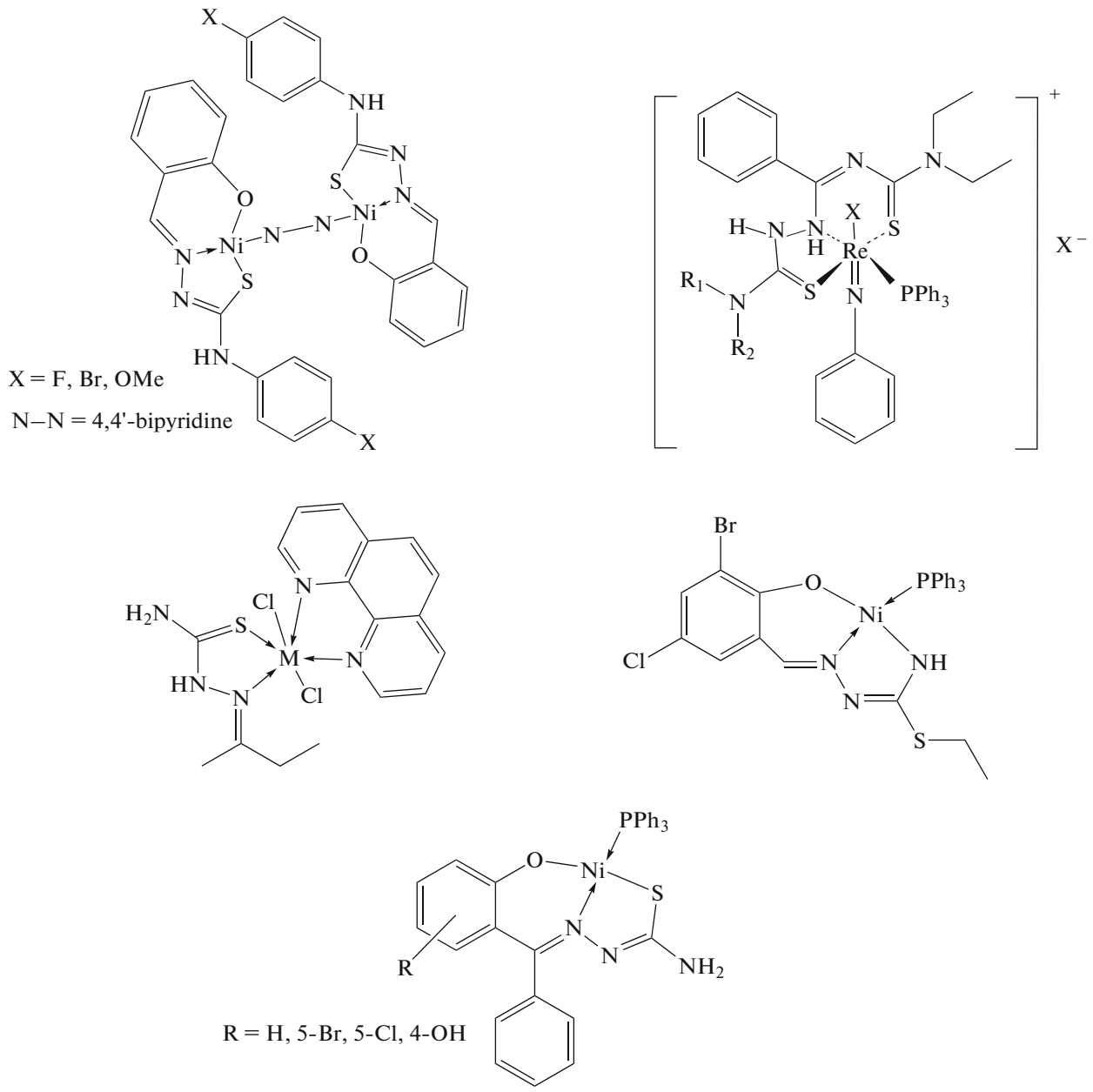
Mixed ligand-metal complexes of thiosemicarbazones. Mixed-ligand complexes have an important role to play in biological systems because mixed chelation occurs commonly in biological fluids as different ligands compete for same metal ions in vivo. Different ligands have different biological activities producing synergetic results and enhancing the potency of the formed complex. These possess specific geometries and have been involved in the storage and transport of active substances through membranes [110]. Mixed-ligand complexes of Cu(II) and Cd(II) with 1,10-phenanthroline and methylethylketone thiosemicarbazone have been reported. The mixed ligand Cu(II) complexes of diimines exhibiting anticancer activity and possessing DNA cleavage activity have also been synthesized along with thiosemicarbazone ligands [111]. The coordination of phenanthroline as coligand enhanced the biological and pharmacological potential of the complexes. Mixed ligand metal complexes with diimine coligand exhibited DNA binding ability in which the diimine coligands played a significant role in the DNA interaction and cleavage mechanism [112].

Metal ions actively participate in many biological processes [113]. Mixed ligand-metal complexes have potential biological relevance. They have been used as metalloenzyme mimics. They also activate enzymes and are involved in storage and transport of active substances [114]. Heterocyclic chemistry is an important branch of organic chemistry. A heterocyclic compound contains at least one hetero atom, like nitrogen, oxygen and sulphur. Most of the drugs are heterogeneous compounds. Heterocyclic compounds have a vital role to play in living systems [115]. Amino acids like proline, histidine, tryptophan, vitamins and coenzyme precursors such as thiamine, riboflavin, pyridoxine, folic acid, biotin, B12 and E families of the vitamins are the most common heterocyclic compounds used in medicine. Ruthenium complexes of diimine ligands such as 2,2'-bipyridine (bpy) and 1,10-phenanthroline (phen) have been used as probes for DNA. The complexes have also shown anticancer properties [116, 117]. The main target has been DNA, still, it is important to search for other targets like enzymes and proteins [118–120]. Other than anticancer activity, the mixed ligand complexes of thiosemicarbazones have also been evaluated for their antibacterial activity. Complexes of Ni(II) with triphenyl phosphine (PPh_3), imidazole, 4-picoline and bipyridine containing 4-(*p*-X phenyl) thiosemicarbazones of salicylaldehyde have been evaluated against *E. coli* and the complex containing 4-picoline was found to be most effective [121]. Mixed ligand complexes of Ni(II), Co(II) and Cu(II) with 2-(1-(2-phenylhydrazono)-propan-2-ylidene)hydrazine-carbothioamide (TPHP) and phenanthroline have been screened against *B. subtilis*, *S. aureus*, *P. aeuroginosa*, *E. coli*, *A. flavus* and *P. italicum*. The structure-activity relationship was also studied to understand the antimicrobial action of the compounds [122]. Zn(II) complexes of 2-acetylpyridine-4-phenylsemicarbazone and N and S containing hetero ligands viz. thiophene, pyridine, picoline, aniline and ammonia have been tested for their antimicrobial activities against *S. aureus, B. anthracis, A. nigers* and *C. albicans* where thiophene and aniline complexes were most active [123]. Eight neutral, ternary, Co(III) complexes of 2-hydroxyacetophenone N(4)-substituted thiosemicarbazones with heterocyclic bases bipyridine, phenanthroline and azide with the general formula [$MLB(N_3)$] have been synthesized and assigned distorted octahedral geometries [124]. Catecholase activity of mixed ligand Mn(II) complex containing Phen has been investigated [125]. Pyridine substituted thiosemicarbazone ligands viz. 2-acetylpyridine thiosemicarbazone, 2-benzoylpyridine *N*(4)-methyl thiosemicarbazone and 2-acetylpyridine *N*(4)-methylthiosemicarbazone and their complexes with Mn, Zn and Co salts have shown significant antitumour activity against K562 leucocythemia cancer cell line [126]. Mixed ligand complexes with amino acids, such as glycine and DL-alanine, have been synthesized. Co(II) and Cu(II) complexes with (±)-5-isopropenyl-2-methylcyclohex-2-enthiosemicarbazone (IPMCHTSC, L1H), 1,7,7- trimethylbicyclo[2,2,1]heptanethiosemicarbazone (TBHSC, L3H) have been tested against *E. coli, S. aureus, P. vulgaris* and fungal strains *A. niger* and *C. albicans* showing improved activity than the uncomplexed ligands [127]. Pd(II) complexes of 4-R-benzaldehyde thiosemicarbazone (R = OCH_3, CH_3, H, Cl^- and NO_2^-) and 1-nitroso 2-naphthol have shown notable catalytic efficiency in C–C and C–N coupling reactions [128]. Aromatic diamines, 2,2'-bipyridine and 1,10-phenanthroline have been used to construct chiral catalysts for stereoselective processes [129]. Heterocyclic bases like phenanthroline and bipyridine and their substituted derivatives disrupt the working of a wide variety of biological systems in the metal-free states as well as in coordinated form. Though the free chelating bases are bioactive, they are usually involved in sequestering trace metals and the resulting metal complexes are the actual active species.

Such metal-ligand complexes have been active against murine leukaemia cell lines and induced apoptosis. Cu(II) complexes containing phen and bpy have exhibited cytotoxicity, genotoxicity and antitumour effects but their mechanistic action is still unknown [130]. Monodentate pyridine ligand and its derivatives also play a vital role in the field of heterocyclic chemistry [131]. Ligands derived from pyridine (Py) when the bond with metals have exhibited potential cytotoxicity. Thiosemicarbazones of 2-acetyl pyridine derivatives have been effective iron chelators and possessed potent antiproliferative activity [132]. Pd and Zn complexes of the same ligand have good antitumour activity [133]. Ru(II) complex with 2-acetyl pyridine thiosemicarbazone is water-soluble and has shown anti-proliferative activity against ovarian carcinoma [134]. Keeping in mind the utility of mixed-ligand metal complexes of thiosemicarbazones, in this study mixed-ligand complexes have been synthesized and tested for their anticancer and antibacterial activity. Pyridine is a nitrogen containing six-membered ring. Pyridine and its derivatives are abundant in nature and play a vital role in heterocyclic chemistry. Pyridine containing compounds have been associated with a variety of biological activities and many of such compounds are in clinical use. They are an important class of compounds for modern medicinal applications. Thiosemicarbazone derivatives containing benzoylpyridine thiosemicarbazones have exerted moderate cytotoxic activity against HuCCA-1, HepG2, A549 and MOLT-3. The compounds also showed potential antimalarial activity [135]. Pt complex with thiosemicarbazones derived from 2-acetyl pyridine and 4-acetyl pyridine have exhibited excellent activity against various human cancer cell lines [136]. Phenanthroline is found in various sex hormones, cardiac glycosides, bile acids and morphine alkaloids [137]. A variety of biological and physiological activities are shown by phenanthroline derivatives making it an interesting moiety. The arrangement of atoms is ideal for providing its potential chelating ability towards various metal ions. Due to the ability of phenanthroline to bind and interact with the DNA, phenanthroline derivatives have been used as therapeutic agents. The polypyridyl and phenanthroline metal-based molecules have been developed as DNA foot-printing agents because of their DNA binding and cleaving properties [138]. Ni(II) complex with 4-methoxy-3-benzyloxybenzaldehyde thiosemicarbazide with N,N-donor phenanthroline and bipyridine [MLB] have been synthesized and tested for antioxidant potential. The prepared complexes were nonmutagenic. The antioxidant potential of the compounds may be due to their nonmutagenic and nontoxic nature. The DNA interaction was also evaluated showing a high binding affinity of the complexes due to the presence of planar ligands [139]. 2,2'-Bipyridine has been widely used for chelating purposes due to its robust redox stability. Bridging ligands comprising two di-2,2'-pyridylmethyl or amino arms have been used to study metal–metal interaction in supramolecular chemistry and for anion-interaction for their use as sensors. The biaryl bond in bipyridyl containing ligands facilitates the metal–metal interaction owing to the conjugated system of the ligand [140]. A series of Schiff based Cu(II) and Zn(II) metal complexes with polypyridyl ligands have been studied for their DNA interactions [141].

Adducts of Cu(II) with thiosemicarbazones and semicarbazones have been synthesized and characterized by different analytical techniques. The adducts exhibited a quasireversible response (DEps100 mV) in cyclic voltammograms at room temperature in *N*,*N*-dimethylformamide, owing to the CuIII/CuII couple. The spectroscopic analysis supported at the irregular octahedral geometry. The nucleolytic cleavage activity was performed on double-stranded pBR322 circular plasmid DNA in the presence and absence of H_2O_2 (an oxidizing agent). In the absence of H_2O_2, a less apparent DNA cleavage was found, and in its presence nuclease activity improved [142].

Novel mixed-ligand nickel(II) complexes {[Ni(L1)(PPh_3)], [Ni(L1)(Py)], [Ni(L2)(PPh_3)]-DMSO, [Ni(L2)(Imz)], [Ni(L3)(4-Pic)] and [{Ni(L3)}2(l-4,40-Byp)]$_2$DMSO of {the 4-(*p*-X-phenyl)thiosemicarbazones of salicylaldehyde} (H2L13) were synthesized taking into account the inductive effect of different substituents (X = F, Br, OCH_3) to know the changes in the biological activity. They were tested against *E. coli* and Bacillus. The fourth compound containing bipyridine ligand showed potential antibacterial activity and could in the future act as a lead molecule for drug design [143]. Some new coordination modes found in mixed ligand-metal complexes of thiosemicarbazones is given as Scheme 9 and some other new mixed ligan-metal complexes of thiosemicarbazones are summarized in Table 2.



Scheme 9.

Homo and heteronuclear complexes of thiosemicarbazones. Dinuclear complexes have been shown to possess interesting structures and hence have been studied for the past few decades [162–165]. In most of the cases, such complexes contain a metal–metal bond which affects the complex's magnetic properties too. It has been well discussed in the course of this study that metal complexes show enhanced biological activity than the free ligand or metal ion. Though substantial work has been done on the synthesis and biological evaluation of mixed ligand complexes but not much work has been reported on mixed metal-ligand complexes which are biologically active and non-toxic. In fact the literature survey reveals almost no work has been taken up on the synthesis and characterization of mixed metal complexes formed by thiosemicarbazone ligands. Some work that is being reported is based on homonuclear dinuclear complexes. A series of mono and dinuclear (η^6-arene) Ru(II) complexes formed by benzaldehyde thiosemicarbazone having the general formula [Ru(η^6-arene)(μ-Cl)Cl]$_2$ have been evaluated for their in vitro cytotoxic effect against WHCO1 (oesophagal cancer cell line) [166]. Neutral dioxovanadium complexes [VO_2(HL)] (H_2L = I : 1, H_2L = II : 2 and H_2L = III : 3;

Table 2. Some new mixed ligand-metal complexes

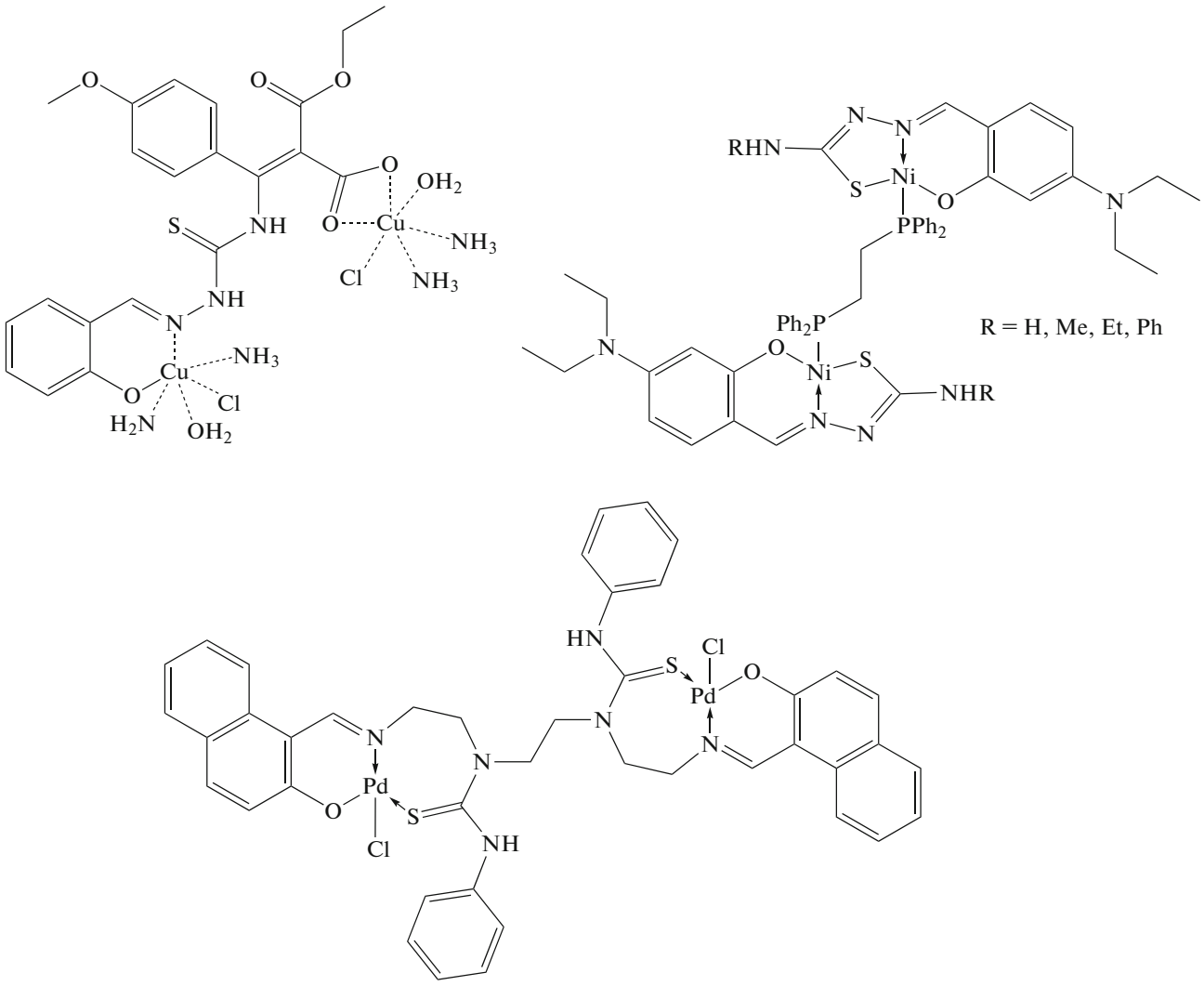
Metal	Thiosemicarbazone	Hetero ligand	Activity	Reference
Cu(II)	5-Bromo-3-methoxysalicylaldehyde-*N*(4)-cyclohexylthiosemicarbazone (H_2Bmct)	1,10-Phenanthroline, 2,2'-bipyridine, 4,4'-dimethylbipyridine, 5,5'-dimethylbipyridine	NA	[144]
Ni(II)	2,4-Dihydroxybenzaldehyde (24D) and 4-methyl-3-thiosemicarbazide (MT24D) or 4-Phenyl-3-thiosemicarbazide (PT24D)	Iimidazole, benzimidazole	Anticancer, Antibacterial	[145]
Ni(II), Cu(II)	2,4-Dihydroxybenzaldehyde-4-phenyl-3-thiosemicarbazone (DHBPTSC).	1,10-Phenanthroline, 2,2'-bipyridine, dppm	Antibacterial, Antifungal, antioxidant	[146]
Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II)	[*N*-(*p*-Tolyl)-2-(3,4,5-trimethoxybenzylidene)hydrazine carbothioamide]	8-Hydroxyquinoline	Antibacterial, antifungal and antimalarial	[147]
Cu(II)	Thiosemicarbazides with *o*-chloroacetoacetanilide	Naphthoic acid	Antifungal	[148]
Cu(II), Ni(II), Fe(II), Zn(II)	2-(Butan-2-ylidene) Hydrazinecarbothioamide	Pyridine, 2,2'-bipyridine	Anticancer, Antimicrobil	[149]
Fe (II), Co(II), Ni(II)	Benzyliminothiosemicarbazone	L-Phenylalanine	Antimicrobial	[150]
Cu(II)	2-(2-Hydroxybenzylidene)-*N*-(prop-2-en-1-yl)hydrazinecarbothioamide	Imidazole (Im), 3,5-dibromopyridine (3,5-Br_2Py), and 4-methylpyridine (4-Pic)	Antimicrobial, antifungal, antioxidant, anticancer	[151]
Ni(II), Ru(II)	Pyridoxal-*N*-allyl-thiosemicarbazone hydrochloride	Triphenylphosphine	Antioxidant	[152]
Co(II), Ni(II), Cu(II)	Salicylaldehyde thiosemicarbazone	Salicylaldehyde phenyl hydrazine	Antimicrobial, antifungal	[153]
Ni(II)	*S*-methyl- or *S*-ethyl-isothiosemicarbazone	Triphenylphosphine	NA	[154]
Cu(II), Ni(II), Co(II)	2-Acetylthiophene thiosemicarbazone	2,2-Bipyridyl	DNA cleavage activity, antibacterial	[155]
Cu(II), Ni(II)	4-Methoxysalicylaldehyde-*N*-phenyl-thiosemicarbazone	3,5-Lutidine	Antioxidant	[156]
Co(III)	*N*-(3,5-bis(Trifluoromethyl)phenyl)pyridine-2-carbothioamide	2,2'-Bipyridine, 1,10-Phenanthroline	Photocatalytic hydrogen generation	[157]
Re(V)		*N,N*-diethyl-*N*'-benzoylthiourea Triphenylphosphan	NA	[158]
Cu(II), Cd(III)	Methylethylketone Thiosemicarbazone	1,10-Phenanthroline	Antibacterial	[159]
Zn(II)	2-(3-Bromo-5-chloro-2-hydroxybenzylidene)-*N*-phenylhydrazinecarbothioamide	2,2'-Bipyridine and 1,10-phenanthroline	DNA binding, anticancer	[160]
Ni(II)	H/5-Bromo-/5-chloro-/4-hydroxy-2-hydroxybenzophenone-thiosemicarbazones	PPh_3	Free radical-scavenging activity	[161]

Table 3. Some new dinuclear thiosemicarbazone complexes

Thiosemicarbazone	Metal	Activity	Reference
Indole thiosemicarbazone	Ru(III)	DNA cleavage, anticancer	[173]
Pyruvaldehydethiosemicarbazone	Zn(II), Tetranuclear/binuclear	DNA binding	[174]
2-Hydroxybenzaldehyde with substituted thiosemicarbazide	Ni, Cu and Zn	Antibacterial and antifungal	[175]
4(*N*,*N*)-Diethylaminosalicylaldehyde-4(*N*)-thiosemicarbazone [H_2-DEAsal-tsc] H_2L^1/4(*N*,*N*)-diethylaminosalicylaldehyde-4(*N*)-methyl thiosemicarbazone [H_2-DEAsal-mtsc] H_2L^2/4(*N*,*N*)-diethylaminosalicylaldehyde-4(*N*)-ethyl thiosemicarbazone [H_2-DEAsal-etsc]	Ni(II), Binuclear	DNA binding, Anticancer	[176]
Methoxy thiosemicarbazone	Co(II), Ni(II), Cu(II), Zn (II)	Antibacterial	[177]
Ferrocenyl substituted thiosemicarbazone ligands	Ru(II)	DNA cleavage, cytotoxicity	[178]
Carvone thiosemicarbazone	Cu(I), Pd(II)	Cytotoxicity	[179]
(*E*)-2-((1H-Indol-3-yl)methylene)-*N*-phenylhydrazine-1-carbothioamide	Ru(II)	Cytotoxicity	[180]
2-Hydroxyacetophenone-*N*(4)-cyclohexylthiosemicarbazone, 2-hydroxyacetophenone-*N*(4)-phenylthiosemicarbazone	Cu(II) Binuclear	NA	[181]
2-Acetyl-3-ethylpyrazine thiosemicarbazides	Bi(III), binuclear	Apoptosis, cytotoxicity	[182]
4-Diethylaminosalicylaldehyde-4(*N*)-substituted thiosemicarbazones	Ni(II), Binuclear	DNA binding, antioxidant activity	[183]
N(4)-Substituted bis(thiosemicarbazone)	Zn(II), Binuclear	NA	[184]
Chromone thiosemicarbazone	Cu(II)	Cytotoxicity	[185]
2-Acetylpyrazine-*N*(4)-methyl thiosemicarbazone	Ni(II), binuclear	Selectivity for dyes	[186]

H_2L are the thiosemicarbazones H_2Pydx-tsc (**I**), H_2Pydx-chtsc (**II**) and H_2Pydx-clbtsc (**III**); Pydx = pyridoxal, tsc = thiosemicarbazide, chtsc = N(4)-cyclohexylthiosemicarbazide, clbtsc = N(4)-(2-chloro)benzylthiosemicarbazide have been evaluated for their antiamoebic activities. The complexes have possessed significant potency against HM1:1MSS strain of *Entamoeba histolytica*. Some of the complexes showed less IC_{50} values than metronidazole [165]. Thiosemicarbazones derived from 2,6-diformyl-*p*-cresol and 4-(X-phenyl) have five donor atoms viz. SNONS and act as pentadentate ligands. They can hold two metal ions nearby without causing steric hindrance. The Cu(II) thiosemicarbazones have been associated with potent antitumour activity [167]. Absorption, distribution, metabolism, excretion and toxicity (ADMET) properties of a typical drug are highly dependent on binding parameters that are useful for understanding protein–drug binding [168]. The reaction of 2-oxo-1,2-dihdroquinoline-3-carbaldehyde 4(*N*,*N*)-dimethylthiosemicarbazone with Cu(II) nitrate yielded $[\{Cu(L)(CH_3OH)\}_2][(NO_3)_2]\cdot H_2O$, which is a water-soluble complex. The complex and the ligand interacted with calf thymus DNA (CT-DNA) and exhibited strong binding to serum albumin. It also showed strong radical scavenging properties and exhibited substantial cytotoxic activity on HeLa, HepG2 and HEp-2 cell lines [169]. Other binuclear Cu(II) complexes derived from cuminaldehyde thiosemicarbazone and substituted thiosemicarbazides $NH_2NHC(S)NHR$, where R = H, Me, Et or Ph have been found to possess good binding ability to calf thymus DNA. The nucleolytic cleavage activity of the complexes was assayed on pUC18 plasmid DNA using gel electrophoresis. The complexes behaved as effective chemical nucleases with H_2O_2 activation [170,

171]. Multinuclear complexes of heavier transition metals have also been evaluated for their properties. Cyclometalated Pt(II) and Ir(III) centres have been prepared using 4,6-diphenylpyrimidine as bis coordinating ligand. N- and C-containing ligands can easily be metallated either simultaneously or in a stepwise manner. The synthetic ease facilitates the formation of homo and heterometallic assemblies having luminescent properties with increased rate constants [172]. These examples show that the binuclear metal complexes having two different metal ions are interesting moieties involving spin-exchange and charge-transfer phenomena. They are also useful as metalloenzymes mimics and are used as homogenous catalysts. Table 3 summarizes some of the recent developments in the field of mixed metal-ligand complexes of thiosemicarbazones. Scheme 10 shows the coordination modes in some mixed metal-ligand complexes of thiosemicarbazones.



Scheme 10.

CONCLUSIONS

Thiosemicarbazones are important examples of Schiff bases having multiple donor atoms like oxygen, nitrogen and sulphur. The presence of these donor atoms assists in complex formation with metals in different oxidation states, particularly with transition metals. The addition of the metal ion to the Schiff base gives the complex unique properties, specially redox properties, which are useful in biochemical redox reactions. Also different types of coordination modes give different geometries to the complexes which can be modified and controlled to help in binding at different biological receptors. Compared to a free ligand,

the metal chelates cross the cell membrane by diffusive mechanism instead of active transport mechanism due to the chelation of the metal ion by the polar regions of the ligands. These properties of the ligand binded metal make these complexes attractive drug targets and several such molecules have been studied in detail, with various ligands and transition metal ions. Although much work has been reported on mononuclear complexes with thiosemicarbazone ligands, less exploration has been made in the development of mixed ligand and mixed metal complexes. To enhance the biological effect, mixed ligand and mixed metal complexes need to be further explored as the mixing of ligands and metals would lead to a possible synergistic effect, thereby enhancing the biological activity. Further studies are also needed to determine whether the ligand and the metal act independently or in unison inside the human body.

This review has provided a detailed account of the recent research conducted in the field of thiosemicarbazone based metal complexes as drug targets. The development of novel complexes as drug targets is required as the existing ones have encountered certain hurdles in their development. Some such problems include the toxicity and hydrophobicity of the complexes that reduce the therapeutic index and in vivo activity of the complexes. Also metal-ion sequestering needs to be remedied as the stable chelation by the thiosemicarbazones may prevent the cell from using the essential metal ions. While several receptors and biological pathways have been identified for the action of these metal complexes, more study is required to discover and explore newer interactions that would help in developing drugs to specifically target different diseases.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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