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RESEARCH ARTICLE

4(N)-ARYL/ALKYL SUBSTITUTED THIOSEMICARBAZONE DERIVED METAL COMPLEXES, THEIR SPECTRAL AND BIOCHEMICAL STUDIES: A REVIEW

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Abstract

N(4)-alkyl/aryl substituted thiosemicarbazones and their metal complexes show significantly enhanced biochemical properties than well-known standard drugs. In this review, we extensively focused on the synthesis, biological applications, and structural characterization of the aforementioned compounds over the past decade. A detailed description of the structures of thiosemicarbazone derivatives substituted at the N(4)-position and their metal complexes is presented here. The structures of the compounds were elucidated with respect to their bonding interactions with metal ions and their geometric configurations. Additionally, the review emphasizes the importance of ligands and complexes by reviewing their biological and analytical applications, such as the newly discovered N(4)-substituted thiosemicarbazones and metal chelates throughout the previous decade. It highlights their potential impact on future research and practical applications.

Introduction:-

Thiosemicarbazide or semicarbazide can be combined with the appropriate aldehydes or ketones to form a class of compounds known as thiosemicarbazones (TSC) and semicarbazones (SC) [1]. Thiosemicarbazone derivatives, having general formulae ($R^1R^2C{=}N{-}NH{-}C(=S){-}NR^3R^4$)(**Scheme 1 (a)**) also exhibit as neutral, monoprotonic, or diprotonic ligand behavior(**Scheme 1 (b)**) [2].A 5-membered chelate ring is provided for transition metal ions by thiosemicarbazones, which have a sulphur atom and an azomethinic nitrogen atom that can act as chelating ligands. The hydrazinic nitrogen atoms can deprotonate following complexation, causing bond delocalization and a lengthening of the C-S bond; as a result, the thione groups in deprotonated thiosemicarbazonato complexes might be considered as "masked" thiolate groups. The sulphur atom's negative charge increases its coordinating power. They typically bond through the sulphur and hydrazinic nitrogen atoms N1 (II) to act as chelating ligands for transition metal ions, while occasionally they act as monodentate ligands and only bond through the sulphur atom (I) [3].However, their ability to act as versatile ligands is enhanced by their easy deprotonation (V), which in certain cases allows them to be N2-mono-N1,S-bidentate (III), bis(S-monodentate) (IV) or S-mono-N1,S-didentate (VI). They may also bond through hydrazine nitrogen N1 and the amide nitrogen, N4 as bidentate ligands (VII) if the sulfur atom is substituted [4].In other instances, the ligands have been observed to act as tridentate species (VIII), leading to a polymeric molecule (IX) when an extra coordinating functionality is nearby the SN donating sites. In general, they can function as N, S-multidentate ligands, and in addition, the binding characteristics and stoichiometries can be altered by incorporating different heteroatoms (such as phenolic or pyridyl) into the backbone

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structure [5]. Thiosemicarbazones are most likely an equilibrium blend of thione and thiol tautomers in solution (**Scheme 2**). The thiol proton is lost to produce a singly charged bidentate ligand, whereas the thione form functions as a neutral bidentate ligand. The complex unit can therefore be cationic, neutral, or anionic depending on preparative conditions, especially pHdependent [6].

(a)

(b)

Scheme 1.(a) Thiosemicarbazones or semicarbazones as chelating ligands; where R^1, R^2, R^3 and R^4 may be H or any other organic substituent; (b) Different binding modes of thiosemicarbazone ligand

Scheme 2. Tautomeric forms of thiosemicarbazones (TSCs) in solution.

The TSC ligands are easily synthesized and their structures can be changed in a number of different ways.A rational design of metal complex stability, redox potentials, membrane permeability, and finally, biological activity is made possible in some circumstances by modest adjustments that have profound effects on the chemistry [7].TSC derivatives are adaptable ligands because they offer enhanced coordination potential, improved selectivity, and stability towards a wide range of metal ions. They can coordinate with different metal ions in a range of distinct coordination modes, including as neutral (keto form) molecules or following deprotonation, as anionic (enol form) ligands [8]. By introducing a donor atom-containing motif to make the ligand polydentate, the chelating ability of

the thiosemicarbazone moiety can be improved [9]. Their effective coordinating nature has been further proven by the binding of ligands even with p-block metal atoms [10].

Thiosemicarbazones (TSCs) are a very significant group of compounds which have potential pharmacological activitiesboth as free ligands and as metal complexes[11].The number of studies on the pharmacology of these compounds has increased significantly since the original work of Domagk's and co-worker's [12, 13] on the anti-tubercular action of metal TSCs and SCs.These compounds have a variety of biological applications that includes, anti-cancer [14], antimalarial [15], antiviral and anti-HIV properties [16], antineoplastic activities [17], antibacterial and antifungal [18], anti-tubercular [19], anti-parasitic activities [20], antitumor [21], antiproliferative [22], anti-oxidant [23], anti-inflammatory and anticorrosion activities [24].By blocking ribonucleotide reductase, an essential enzyme for the creation of DNA precursors, thiosemicarbazones exert their biological activity in mamalian cells [25]. TSCs primary mode of action is its ability to chelate with a wide variety of metal ions to produce stable organometallics, which increase their cytotoxic effects on living cancer cells and significantly contribute to their anticancer effect [26]. According to the study, their anticancer properties are mostly attributed to their capacity to inhibit the following three target locations. (i) The enzyme ribonucleotide reductase, which is involved in the rate-limiting phase of DNA synthesis, is inhibited by thiosemicarbazone derivatives [27]. (ii) These substances stabilize the cleavable complex between topoisomerase II and DNA through thiol alkylation, which inhibits topoisomerase II.(iii)It has recently been discovered that TSCs inhibit ATP binding cassette (ABC) transporters, which are well known to be crucial in the emergence of multidrug resistance [28].

Alongside their variety of biological activities TSCs have also been used for tumor imaging, perfusion imaging of the brain and heart, and the assessment of cerebral and myocardial blood flow using positron emission tomography (PET) imaging with copper isotopes [29]. TSCs and their metal complexes reveals their use as acatalysts in several organic transformations [30], including coupling reactions [31]. The selective and particular coordination characteristics of TSCs make them promising as metal ion sensors and for the scavenging of metals [32].TSCs have also been used in the spectrophotometric study of various metals due to their capacity to generate intensely colored complexes with different metal ions [33].

DNA Binding/Cleavage Properties

A series of Zn(II) ferrocenylthiosemicarbazone complexes**(1-4)** made from thiosemicarbazide and 4-methyl-, 4-ethyl-, and 4-phenyl-3-thiosemicarbazide were presented here by Rajamuthy, Vikneswaran, et al. Obtained compounds were characterized by CHN/O analyser, infrared, electronic, fluorescent spectral techniques, Cyclic voltammetric measurements and X-ray crystallography. Viscosity measurements were performed on CT DNA by altering the concentration of the added complexes in order to comprehend the nature of the complexes' DNA binding. The compounds do not intercalate into CT DNA nucleobases, as demonstrated by viscosity studies. At extremely low concentrations, they cleave supercoiled DNA into linear circular forms and display effective nuclease activity in the absence of an activating factor [34].

Yousef, Tarek A., et al. conducted an experimental and computational investigation on new Cr(III), Fe(III), Co(II), Hg(II), and U(VI) complexes of (E)-2-((3-hydroxynaphthalen-2-yl)methylene)-N-pyridin-2-yl)hydrazinecarbothioamide (H_2L). The ligand and its complexes were studied by elemental analysis, spectroscopic studies, magnetic and thermal studies. The synthesized Schiff-base exhibits thiol–thione tautomerism and acts as a

mononegative bidentate ligand N,O donor via azomethine N, deprotonated naphtholic–O, or via azomethine N and thio S. All complexes were indicated to have octahedral structures, with the exception of Hg(II), which is tetrahedral. Calculation of molecular parameters, including electronegativity, net dipole moment, heat of formation, and binding energy, indicates that metal complexes are more stable than ligands. A low ΔE value signifies that ligand molecules are more likely to interact with metal ions. The Coats-Redfern and Horowitz-Metzger techniques were used to derive kinetic and thermodynamic parameters for various decomposition processes. Complexes Fe (III) **5**and Cr (III)**9** were shown to specifically cleave DNA isolated from Calf-Thymus, indicating their potential as nuclease agents. Because the compound was found to cleave DNA, it hinders the growth of harmful organisms by cleaving their genomes [35].

The authors in this study have described the synthesis of palladium and platinum metal complexes with 1,3,5-triaza-7-phosphaadamantane (PTA) acting as a co-ligand and 5-nitrofuryl-containing thiosemicarbazones (L) acting as bioactive ligands against T. cruzi. Eight novel complexes**10-17** of the formula [MCl(L)(PTA)] with M = Pd or Pt were synthesized and characterized with the majority of the complexes exhibiting comparable anti-T. cruzi activity to the corresponding free thiosemicarbazone ligands. The prepared metal complexes containing the phenylthiosemicarbazone derivative exhibited highest activity, were non-toxic to mammalian cells, and had selectivity indices of over 10-20. ESR spectroscopy studies demonstrated that parasites may decrease ability of the complexes, resulting in hazardous free radical species such as $^{\bullet}OH$ and nitroanion. Gel electrophoresis and fluorescence tests indicate that the complexes interact with DNA in an intercalating manner, although this is not the primary mechanism of their anti-T. cruzi effect. The results suggest that complexing bioactive ligands with chosen metals is a viable technique for creating better metal-based antiparasitic drugs [36].

New tetranuclear $[Pt_4(Am_4M)_4]\cdot 16.25H_2O$ complex **18** of (Z)-2-(amino(pyridin-2-yl)methylene)-N-methylhydrazinecarbothioamide (H_2Am_4M) were synthesized and characterized using a variety of physico-chemical methods by Shao, Jia, and co-workers. Strong intramolecular π–π stacking stabilizes the tetranuclear unit, resulting in an eight-membered ring $[Pt_4S_4]$ that resembles a ship and has four tridentate ligands peripherally coupled to four

Pt(II) ions. UV and fluorescence spectroscopy techniques were used to investigate the DNA and protein binding characteristics of complex (1). Viscometric measurements validated the efficient DNA intercalative binding mode suggested by the binding constant and apparent binding constant to calf thymus DNA (CT-DNA), which were properly fitted by two respective non-linear equations. Complex 1 may have an effective nuclease activity on DNA, as evidenced by agarose gel electrophoresis tests that show complex 1 may completely digest the plasmid DNA pUC19. Inhibitors of singlet oxygen ($^1O_2$) demonstrated an inhibitory impact on the cleavage. Additionally, complex 1 showed a medium affinity for bovine serum albumin (BSA) at various temperatures, which was speculated to be due to a static binding mode by fluorescence spectrometry. The poly-Pt(II) complex may have biological activity as a possible chemotherapeutic drug, based on all of these findings [37].

Four new complexes [Pd(Msal-tsc)($AsPh_3$)] **19**, [Pd(H-Msal-mtsc)($AsPh_3$)] **20**, [Pd(H-Msal-etsc)($AsPh_3$)] **21**and [Pd(Msal-ptsc)($AsPh_3$)] **22** were synthesized from the reaction of 4(N)-substituted 3-methoxysalicylaldehyde thiosemicarbazone (H_2L1–H_2L4) ligand with [PdCl2($AsPh_3$)$_2$] by Kalaivani, P., et al. According to X-ray crystallography, the ligands H_2L2 and H_2L3 form a five-member chelate ring in complexes **20** and **21**, where they coordinate as monobasic bidentate NS donors. But in compound **22**, the ligand H_2L4 formed six and five member chelate rings when it attached to palladium as a dibasic tridentate ONS donor. Photophysical investigations were conducted to study the interactions between ligands (H_2L1–H_2L4) and their corresponding complexeswith calf-thymus DNA (CT DNA). The results showed that the complexes bind to DNA through intercalation mechanism. The novel palladium (II) complexes demonstrated superior binding activity among them, surpassing both their parent complex [$PdCl_2(AsPh_3)_2$] and its corresponding ligand in the comparison of their binding ability with CT DNA/BSA whereas complex **21** was the most efficiently bound [38].

Cobalt (III) complexes with pyridoxal N(4)-substituted thiosemicarbazone ligands have been synthesized by Manikandan, Rajendran, et al. from the reaction of [$CoCl_2(PPh_3)_2$] and pyridoxal N-methyl-thiosemicarbazone hydrochloride /pyridoxal N-phenyl-thiosemicarbazone hydrochloride. The twisted octahedral geometry surrounding the metal ion with two ligand molecules was revealed by the molecular structure of complex **24**, which was examined using X-ray crystallography. Potential biological activities of the newly synthesized complexes, including protein binding, antioxidant activity, cytotoxicity, and DNA binding and cleavage, were investigated. The ability of both complexes to bind to DNA via intercalation was assessed using fluorescence spectroscopy, and it was shown that complex **24** was able to bind to DNA more strongly than complex **23** because of the phenyl substitution in thiosemicarbazone. In comparison to the ligands, the complexes also demonstrated enhanced radical scavenging abilities and conventional antioxidant properties. It was discovered that the substitution of the phenyl ring at the

ligand's thiosemicarbazone enhances the degree of cytotoxicity by linking the activity of the complexes with their substitution of thiosemicarbazone [39].

Netalkar, Priya P., Sandeep P. Netalkar, and Vidyanand K. Revankar successfully prepared and characterized air- and moisture-stable coordination compounds of late first row transitionmetals, i.e. Co(III)**25**, Ni(II)**26**, Cu(II)**27**, and Zn(II)**28**, derived from the ligand (E)-4-(4-chlorophenyl)-1-(1-hydroxypropan-2-ylidene)thiosemicarbazide. The molecular structures of the ligand LH and complexes C1 and C2 were definitively determined by X-ray diffraction. A meridonial pattern of thiolate sulfur atom, azomethine N, and hydroxyl OH forms two stable five-membered rings in complex C1, indicating that the ligand coordinated as a tridentate donor. On the other hand, the ligand in complex C2 coordinated via the hydroxyl OH, azomethine N, and thione sulfur atom. It is discovered that complex C3 exhibits a quasi-reversible redox process and is electrochemically active in the working potential range. Viscosity, heat denaturation, and electronic absorption spectroscopy were used to examine how each drug interacted with calf thymus DNA thoroughly. The findings of the experiment demonstrated that complexes C1, C2, and C3 bind electrostatically to CT-DNA, whereas the ligand and complex C4 can bind partially through intercalation. The gel electrophoresis investigation further confirms the significant binding and cleavage affinity of the C1, C2, and C4 complexes towards the DNA of E. coli. The findings have significance for the advancement of late first row transition metal-based complex design and development, as well as the methodical evaluation of DNA binding and cleavage activity for possible therapeutic agent applications [40].

Matesanz, Ana I., Sandra Tapia, and Pilar Souza discuss the preparation and characterisation of the 3,5-diacetyl-1,2,4-triazol mono(4-phenylthiosemicarbazone) ligand, H_3L, and its derived palladium(II) and platinum(II)

complexes, [Pd(HL)(PPh_3)]**29** and [Pt(HL)(PPh_3)]**30**. By using single-crystal X-ray diffraction, the chemical structures of the two novel metal complexes have been ascertained. The metal ion in both complexes is four-coordinated with a [N_2SP] donor environment through one triazole N atom, the thione S and azomethine N atoms of the thiosemicarbazone moiety, and a P atom from the PPh_3 co-ligand. Human cancer cell lines T-47D, A2780, and A2780cisR were used to test the cytotoxicity of the newly synthesized compounds in vitro; H3L exhibited the highest level of activity among these species. The results show a pronounced negative impact on cytotoxicity when Pd or Pt center is introduced into the ligand environment. One probable explanation has to do with the structural alterations brought about by complexation, such as the existence of large triphenylphosphine groups that sterically restrict interactions between metals and DNA and inhibit direct hydrogen bonding with biological molecules. Moreover, UV–Vis absorption spectroscopy was used to investigate H3L's capacity to bind DNA with calf thymus DNA [41].

By Bedier, R. A., et al., an entirely novel group of compounds were produced from the novel ligand 4- (2-pyridyl) - 3-thiosemicarbazide and benzil α-monoxime (H_2DPPT) which were characterized by spectroscopic methods. The infrared spectrum data indicates that H_2DPPT coordinates as the mononegative NNS tridentate, the binegative NNSN tetradentate, and the neutral NN bidentate to the metal ions. The geometry of the ligands and their studied complexes was confirmed by the calculations of the bond length, bond angle, HOMO, LUMO, and dipole moment based on the modeling investigations. Following conformational analysis and geometry optimization, spectral investigations are perfectly in accord, allowing the precise structure of every complex under study to be suggested. Complex stability was clarified, and the Coats-Redfern and Horowitz-Metzger methods were used to assess the kinetic parameters (E, A, ΔH, ΔS, and ΔG) of each thermal degradation step. Consequently, the metal complexes are determined to be semiconducting materials with computed electronic characteristics. The antibacterial efficacy of the ligand and its metal complexes against the bacterial species Bacillus thuringiensis, Staphylococcus aureus, Pseudomonas aeuroginosa, and Escherichia coli was tested, demonstrating the greater potency of metal complexes over ligands. Additionally, tests on the compounds under investigation's degradation effect revealed that the Ni complex**31** had a strong and thorough degradation effect on DNA [42].

Trivalent cobalt complexes of hydrazinecarbothioamides produced from 4-(propan-2-yl) benzaldehyde and substituted thiosemicarbazides NH2NHC(S)NHR, where R = H, Me, Et, or Ph have been described by Panchangam, Murali Krishna. Numerous physicochemical approaches, such as elemental analysis, molar conductance, magnetic susceptibility tests, IR, electronic absorption spectral investigations, and cyclic voltammetry, were used to characterize the produced ligands and complexes. Complexes are diamagnetic, low spin octahedral cobalt(III) complexes, according to the magnetic susceptibility data. According to the absorption titration experiments, calf thymus DNA is readily bonded to all of these complexes**35-38**. Appearing binding constants range from 107 to 108 M-1. Gel electrophoresis was used to test the ligands' and their complexes' nucleolytic cleavage activity on pUC18 plasmid DNA in both the presence and absence of H_2O_2. Under cobalt complex administration, the ligands exhibited enhanced nuclease activity. Hydrogen peroxide activation makes all of the complexes function as effective chemical nucleases. These investigations demonstrated that the complexes display both hydrolytic and oxidative chemistry during DNA cleavage [43].

Aly, Samar A. synthesized and described a novel class of Ru(III)**39**, Pd(II)**40**, and Co(II)**41** complexes with thiosemicarbazone ligands. Tetrahedral geometry for Ru(III), Co(II) complexes, and square planar geometry for Pd(II) complexes have been proposed based on FTIR, UV-Vis, 1H NMR spectroscopic characterization, molar conductivity, magnetic, thermal, and elemental analysis studies. Pd(II) complexes have a higher thermal stability than Ru(III) complexes. In comparison to the palladium complexas a quencher, fluorescence binding of the complex with DNA molecules did not demonstrate any fluorescence quenching capabilities. The exceptional antibacterial activity of these compounds was explained by the antibacterial investigations conducted on the synthesized ligand (H_2L_2) and its metal complexes, which were screened against pathogenic microorganisms [44].

Shanmugapriya, A., F. Dallemer, and R. Prabhakaran explored a series of novel Pd(II) complexes **42-45** which were produced from the reactions between $K_2[PdCl_4]$, 3-methoxysalicylaldehyde–4(N)-substituted thiosemicarbazone

[H_2L1–H_2L4], and 1,3-bis(diphenylphosphino)propane [dppp]. Every complex was identified using a variety of spectroscopic methods, and single crystal X-ray diffraction was used to ascertain the crystal structures of complexes **43** and **45**. The thione sulfur atom of the H2L2 ligand was present at the fourth site of compound **43**, which is a mononuclear compound with ONS chelation of the ligand. In contrast, complex **45** has a single crystallographic unit cell that houses two separate units. By employing UV-vis and fluorescence emission spectroscopy, the binding affinity and behavior of the palladium complexes against calf-thymus (CT) DNA and BSA (bovine serum albumin) were investigated. Based on the outcomes of the DNA binding investigations, it can be inferred that the complexes demonstrated a noteworthy propensity for binding and that their contact with DNA occurs via electrostatic interaction. Complexes **43** and **44** demonstrated considerable cytotoxicity when the compounds' in vitro cytotoxicity was assessed against the MCF-7 (human breast cancer) cell line by comparison with cisplatin [45].

Rajendran, Neelaveni, et al. synthesized and used spectro-analytical methods to identify the structure of nine novel thiosemicarbazone copper(II) complexes from 4-methoxy-1-naphthaldehyde, N(4)-substituted thiosemicarbazide derivatives and diimine co-ligands (phen/bpy). An EPR research revealed that thiosemicarbazone copper(II) complexes had a square planar shape due to the presence of two deprotonated thiolic sulfur molecules. Cu(II) complexes resulting from thiosemicarbazone ligands were evaluated biologically by analyzing their DNA-cleavage, antibacterial activity, and in vitro cytotoxicity. The results showed that, at a concentration of 60 mM, complex **48c** had the maximum DNA-cleavage efficiency and the strongest antibacterial activity of the nine. Furthermore, compared to all the other complexes, **48c** demonstrated a significant cell-killing effect on HeLa cell lines through in vitro experiments. Therefore, with additional investigations into the pathway implicated in the mechanism of action, the powerful compound 9 may be used as a novel, effective anticancer medication [46].

Sodium(E)-4-hydroxy-3-((2-(pyridin-2-ylcarbamothioyl)hydrazineylidene)methyl) benzenesulfonate (NaH_3PyTSC) and its cobalt(II)**49**, nickel(II)**50**, and copper(II)**51** chelates have been obtained by Fetoh, Ahmed, et al., and their

structures were determined using a variety of spectroscopic techniques along with the photoactivity of compounds. The spectroscopic experiments show that the NaH_3PyTSC ligand functions as a bi-negative NOS tri-dentate and a bi-negative NNSO tetradentate, resulting in a tetrahedral geometry for both $[CoH_2PyTSC(H_2O)]_2.2H_2O$**49**, $[CuH_2PyTSC(H_2O)]_2.H_2O$**51** complexes with two unique octahedral and tetrahedral geometries for $[NiH_2PyTSC(H_2O)]_2.4H_2O$**50** complex. The ligand exhibited maximal luminescence at 19960 cm-1, while all complexes emit at 28409 cm^{-1}, indicating photoactivity. Several descriptors, including HOMO, LUMO, MEP, and theoretical IR, have been estimated using DFT optimization. Antibacterial, antifungal, DNA bioassay, antioxidant, and anticancer properties of the isolated frameworks were investigated [47].

Two novel copper (II) substituted thiosemicarbazone Schiff base complexes, $[Cu(L_1)(\mu\text{-}SCN)]n(NO_3)_2$**52a** and $[Cu_2(\mu\text{-}SCN)(SCN)(L_2)_2](NO_3)$ **52b**, were synthesized by Biswas, Niladri, et al. by condensation substituted thiosemicarbazides such as 4-methyl-3-thiosemicarbazide or 4-ethyl-3-thiosemicarbazide with 2-acetylpyridine. IR, UV-Vis, and ESR spectroscopy were among the spectroscopic methods used to characterize both metal complexes, which were then subjected to elemental analysis, CV measurement, and single crystal X-ray structural analysis. In the square pyramidal coordination geometry surrounding Cu(II), the thiosemicarbazone Schiff base ligand coordinates in a tridentate manner. Protein molecules (BSA and HSA) and CT-DNA were used as models to assess the possible binding capacities of the complexes. Effective DNA propensity was demonstrated by both complexes. Using DNA and protein molecules (BSA and HSA), a molecular docking analysis was used to determine the precise mechanism of action of Cu (II) complexes. In comparison to their controls, both the complexes exhibit stronger anti-proliferative and anti-apoptotic properties. When assessing AGS and A549 to their control cells, complexes substantially increase the sub-G0 phase on these cells. Complex **52b** appears to be a more effective anti-apoptotic drugs than complex **52a**, yet both complexes show anti-apoptotic action when it comes to apoptosis [48].

A new thiosemicarbazone ligand, 1-(di(pyridin-2-yl)methylene)thiosemicarbazide (HL), and its Mn(II) complex**53**($MnL_2.H_2O$), were synthesized and studied by Amritha, B., and colleagues. Studies using single-crystal X-ray diffraction showed that two distinct $Mn(L)_2$ molecules, two water molecules of crystallization, and a DMF molecule were present in the asymmetric unit of the triclinic unit cell. Viscosity measurements, fluorescence intercalator displacement tests, and absorbance titrations were used in DNA binding investigations of the ligand and its complex. It was discovered that the complex and the ligand both had strong DNA binding properties and actively replaced the common intercalator, ethidium bromide. With a Kb value of 1.032 x 105, the ligand demonstrated an intercalating mode of DNA binding. Apart from the investigations on DNA binding, the antibacterial properties of

both the ligand and the complex were ascertained and evaluated. The manganese complex**53** also demonstrated an intriguing characteristic: colorimetric sensing. This characteristic allows for the probe to be used as a visual aid for the detection of Fe^{2+} and Ru^{3+} ions, as it changes color from yellow to colorless. In conclusion, the ligand 4-phenyl-1-(di(pyridin-2-yl)methylene)thiosemicarbazide (HL) and $MnL_2.H_2O$ has significant biological activity, including $MnL_2.H_2O$ exhibits outstanding DNA binding, antimicrobial, and visual colorimetric sensing characteristics [49].

Using a range of spectroscopic and analytical methods, Rajendran, Neelaveni, et al. have synthesized and characterized nine mixed-ligand copper(II) complexes, comprising three sulfur-containing ligands and two diimine co-ligands, such as 2,20-bipyridyl and 1,10-phenanthroline. A single deprotonated ligand and the N,N,O-donor of the bidentate ligand ensure the square planar coordination of the mixed-ligand copper(II) complexes**55a-c**, whereas two deprotonated ligands coordinate the copper(II) bis complexes**54a-c**. Furthermore, the disc diffusion technique, agarose gel electrophoresis, and MTT test have been used to explore the biological roles of the produced compounds. Interestingly, oxidative breakdown of the mixed ligand thiosemicarbazone copper(II) complexes with phen results in a greater DNA binding than the other complexes. Remarkably, because the thioamide and phen moiety of heteroaromatic complexes had distinct substituents, they possessed potential biological activity as compared to copper(II) bis complexes. This investigation led to the conclusion that mixed-ligand copper(II) complexes may make useful chemotherapy medications [50].

Salicylaldehyde-based thiosemicarbazone derivatives found in half-sandwich Ru, Rh, and Ir complexes were synthesized, characterized, their bonding mechanisms, and their antibacterial and antioxidant properties were studied by Dkhar, Lincoln, et al. Three mononuclear and six binuclear cationic compounds were formed using chloride, PF_6, or both as counter ions. According to single-crystal X-ray diffraction studies, TSC ligands coordinated as ruthenium mononuclear coordination and rhodium and iridium di-nuclear coordination, the results are supported and validated by mass spectra of all ruthenium, rhodium, and iridium complexes. The results of an antibacterial investigation showed that although TSC ligands, rhodium and iridium binuclear complexes, shown strong activity against both gram-positive and gram-negative bacteria, mononuclear ruthenium complexes showed no action at all. In comparison to other samples, the antioxidant study's findings demonstrated the higher activity of ligand L2, complexes **56a** and **56b** both ruthenium complexes. DNA binding experiments on complexes **56a** and **57a** using SM-DNA reveal no appreciable spectral changes in peak shift or intensity, indicating that these complexes do not bind to Salmon milt's DNA helix [51].

By using spectrometric techniques, Beebe, Stephen J., et al. synthesized and studied the Co (III) complexes of 9-anthraldehyde-N(4)-methylthiosemicarbazone (MeATSC) and phenanthroline ligand. UV-visible spectrophotometric analyses were performed to examine the interaction between complex **58** and calf thymus DNA (ct-DNA). While Complex **58** exhibits strong inhibition of human topoisomerase I and IIα, it interacts with ct-DNA weakly. When it came to 4T1-luc cells, the complex exhibited mild cytotoxic effects, while the "free" ligand and precursor did not significantly limit proliferation. It has been demonstrated that Complex **58** causes the mitochondrial membrane potential to dissipate and causes apoptosis. However, the reduction in 4T1-luc cell viability when the caspase inhibitor z-VAD-FMK is present indicates a noteworthy caspase-dependent aspect of cell death. According to the obtained results, cobalt(III) complexes should be further investigated for potential anticancer therapeutic applications [52].

Savir, Savina, et al. synthesized several Ni(II) metal complexes with formulae $[Ni(L_1)PPh_3]Cl$**59a**, $[Ni(L_2)PPh_3]Cl$**59b**, $[Ni(L_3)PPh_3]$ **59c**, and $[Ni(L_4)PPh_3]$ **59d** and were characterized by spectrochemical and X-ray diffraction method. The Schiffbase ligands, through their tridentate O, N, and S atoms, attach to the metal center of the complexes, which have a square planar shape and four coordinations. When evaluated against human colorectal cancer HCT 116, ligand L_2 and complex **59a** had stronger cytotoxic activity than cisplatin, with IC_{50} values of 5.75 ±0.49 and 4.26 ±0.29 μM, respectively. Furthermore, complex **59c** was discovered to have higher levels of cytotoxic activity against in comparison to its ligand L_3. Conversely, complexes **59b** and **59c**demonstrated a modest level of in vitro antimalarial activity, with respective IC_{50} values of 9.88 ±0.23 and 1.06 ±0.01 μM. Complexes **59b** and **59c**have been predicted by molecular docking simulation to be a minor groove binder with a notable affinity for DNA binding. This suggests that the cytotoxicity and antiplasmodial activity of complexes **59b** and **59c**were likely mediated by their interactions with DNA base pairs through the benzaldehyde, triphenylphosphine, aliphatic chain, and phenyl moieties [53].

A group of researchers led by Akl, Magda A., Mohammed MH Al-Awadhi, and Abdelrahman S. El-Zeny prepared a novel thiosemicarbazide, which they called 2,2'-(9,10-dihydro-9,10-ethanoanthracene-11,12-dicarbonyl) bis (N-allyl hydrazine-1-carbothioamide). The synthesiszed compounds were analyzed by spectrochemical methods like

Elemental analysis, IR, mass, and ^{1}H, ^{13}CNMR. Moreover, metal complexes synthesized by combining with Co^{2+}, Ni^{2+}, and Cu^{2+} acetate salts were then measured for elemental, spectral, mass, molar conductivity, and magnetic moments. IR data revealed that TSc chelates exist as neutral O,N in mononuclear Co(II) complexes, binegative $O_2N_2S_2$ hexadentate in binuclear Ni (II)**61** and Cu (II) **62**complexes, or as a mononegative O,N neutral chelate in keto-thione form. The Zn^{2+} complex exhibited a tetrahedral geometry, whereas other complexes provided an octahedral environment. The geometry of all compounds was drawn using the DFT approach, and factors such bond lengths, bond angles, dipole moment, Frontier orbitals (HOMO, LUMO), MEP, and energetic parameters (optical energy gap, softness, hardness, electronegativity) were analyzed. Additionally, the compounds were tested for DNA binding and SOD antioxidant properties. TSC, a thiosemicarbazide ligand, shown strong antioxidant activity, including DNA binding and SOD-like activity. It is comparable to the standard and has the ability to intercalate DNA effectively. The SOD mimic activity experiment showed that TSC (potent activity) and Co(II)**60** and Ni(II)**61** complexes are effective SOD mimic scavengers, equivalent to ascorbic acid, the standard medication. These compounds have potential for use as antioxidants and anticancer medicines [54].

Pelosi and colleagues synthesized and analyzed four novel thiosemicarbazone compounds, naphthaldehyde and anthraldehyde, and their copper complexes using X-ray diffraction for application in biological system interaction investigations. Unexpected oxidation products and the separation of Cu(I) metal complexes resulted from these ligands' reactions with Cu(II) salts. Out of two Cu(I) complexes, only $[CuI(L_1)_2](HSO_4)$ **63a**remained stable in the studied conditions and did not suffer reoxidation. As a result, it and its parent ligand were chosen for additional biological studies. Both the ligand and its complex demonstrated DNA binding. There was little variation in the behavior of the ligand and the complex, despite the fact that both exhibited an affinity for BSA. This was most likely caused by the thiosemicarbazone moiety of the substances that interacted with the protein [55].

Cytotoxic Properties

C. Priya Varma *, K. Subin Kumar, and K. K. Aravindakshan successfully synthesized complexes of Fe(III)**64**, Co(II)**65**, Ni(II)**66**, Cu(II)**67**, and Zn(II)**68** using isatin N(4)-methyl(phenyl)thiosemicarbazone (ISTSC). The ligands and complexes were characterized using a variety of physicochemical methods, including the CHNS analyzer, ^{1}H-NMR, IR, UV-Vis spectroscopy, and magnetic susceptibility assessments. The presence of N,N,S or O,N,O donor atoms is a defining property of these compounds with carcinostatic activity. The antibacterial activity of the metal complexes and isatin- N(4)-methyl(phenyl)thiosemicarbazone revealed that the complexes excelled the free thiosemicarbazone ligand. The ability of all the complexes and the ligand to kill cancer cells, even at low concentrations, was determined by testing their in vitro cytotoxicity against Ehrlich's Ascites Carcinoma (EAC) and Dalton's Lymphona Ascites (DLA) cell lines. Specifically, the Cu(II) complex**67**, [CuL]Cl.H_2O, with an IC_{50} value of 38 µg/ml, demonstrated increased cytotoxicity against the aforementioned cancer cell types. Thus, at a medium concentration, it has demonstrated the potential anticancer effect of the copper (II) complex **67** of isatin N(4)-methyl(phenyl)thiosemicarbazone [56].

Palladium(II) bis-chelate complexes of class [Pd(TSC^{1-5})$_2$] **69a-e** were synthesized by Hernández, Wilfredo, et al. with combining 4-phenyl substituted thiosemicarbazone ligands, and spectroscopic techniques like IR, ^{1}H-, and ^{13}C-NMR were used to characterize them. With the help of single-crystal X-ray crystallographic techniques, the molecular structures of $HTSC^{3}$, $HTSC^{4}$, and [Pd(TSC^{1})$_2$] **69a** have been identified. Complex whereas other complexes provided an octahedral environment. The geometry of all compounds was drawn using the DFT approach, and whereas other complexes provided an octahedral environment. The geometry of all compounds was

drawn using the DFT approach, and whereas other complexes provided an octahedral environment. The geometry of all compounds was drawn using the DFT approach, and whereas other complexes provided an octahedral environment. The geometry of all compounds was drawn using the DFT approach, and whereas other complexes provided an octahedral environment. The geometry of all compounds was drawn using the DFT approach, and whereas other complexes provided an octahedral environment. The geometry of all compounds was drawn using the DFT approach, and whereas other complexes provided an octahedral environment. The geometry of all compounds was drawn using the DFT approach, and whereas other complexes provided an octahedral environment. The geometry of all compounds was drawn using the DFT approach, and whereas other complexes provided an octahedral environment. The geometry of all compounds was drawn using the DFT approach, and whereas other complexes provided an octahedral environment. The geometry of all compounds was drawn using the DFT approach, and whereas other complexes provided an octahedral environment. The geometry of all compounds was drawn using the DFT approach, and **69a** has a square planar shape and two deprotonated ligands that are cis-arranged and bound to Pd(II) via the azomethine N and thione S atoms. The six human tumor cell lines (H460, DU145, MCF-7, M14, HT-29, and K562) were used to test the ligands made from thiosemicarbazones and their corresponding palladium(II) complexes for their ability to be cytotoxic against cisplatin under the same experimental settings. With the exception of $[Pd(TSC^1)_2]$**69a**, all palladium(II) complexes were more cytotoxic against all examined human tumor cell lines than cisplatin (IC_{50} = 2.85−7.60 μM). A key factor in enhancing the antiproliferative action of benzene and naphthalene aromatic rings is the presence of 3-hydroxy and 1-nitro substituent groups. In comparison to the other complexes and the free ligands, the hydroxy-substituted $[Pd(TSC^3)_2]$ **69c** complex proved to be more lethal in all tumor cell lines at low micromolar dosages [57].

The structural properties of manganese complexes formed from 2-acetylpyridine-N(4)-R-thiosemicarbazones (Hatc-R) were studied to find compounds with strong anti-Mycobacterium tuberculosis action. DFT simulations were used by Oliveira, Carolina G., et al. to assess the impact of thiosemicarbazonate ligands on complex charge distribution and verify Mn-donor bond dissolution. The results show that the thiosemicarbazone ligands coordinate in a monoanionic N,N,S-tridentate manner, producing octahedral complexes of the kind $[Mn(atc\text{-}R)_2]$**70a-f**, which are paramagnetic in the presence of five unpaired electrons. The peripheral substituent groups at the N4 position of the atc-R1− ligands have an impact on two nearly reversible processes that are shown by the electrochemical investigations. To identify their selectivity index, the minimum inhibitory concentration (MIC) of these drugs against M. tuberculosis and their in vitro cytotoxicity on VERO and J774A.1 cells (IC_{50}) were measured. It was found that the compounds have the potential to be effective anti-M. tuberculosis agents, with SI values on par with or better than those of several commercially marketed TB treatments [58].

Nguyen, Thi Bao Yen, et al. communicated, the synthesis of stable complexes of Ni^{2+}, Pd^{2+} and Pt^{2+} and ReO^{3+} metal centers with benzamidine/thiosemicarbazone hybrid ligand H_2L. The ligand H_2L is deprotonated twice and combines with the central meal ion through the N_2S_2 donor set in all complexes. The coordination spheres of compounds **71**, **72**, and **73** are distorted square-planar, however, compound **74** of rhenium is an octahedral trans oxido/methoxido complex. Some antiproliferative effects on human MCF-7 breast cancer cells are demonstrated by the proligand H_2L and its oxidorhenium(V) complex. With an IC_{50} value of 21.1 µM, the H_2L proligand exhibits medium cytotoxicity. The nickel**71**, palladium**72**, and platinum**73** complexes are essentially inert, but the rhenium complex **74** has a higher antiproliferative action (IC_{50} = 5.52 µM). Research with further derivatives of this class is advised, as H_2L is now the sole representative of this novel family of potentially bioactive hybrid ligands [59].

The cytotoxic properties of acetoacetanilide N(4)-methyl(phenyl)thiosemicarbazone (L_2H) and its seven distinct metal complexes were investigated by Priya, N. P., et al. Elemental analysis, magnetic moment measurements, infrared, UV/Vis spectra, and 1H NMR spectral analyses were used to describe the ligand and the complexes. The DLA cell line was significantly cytotoxically affected by the ligand AcTSC and its Fe(II)**75**, Co(II)**76**, Ni(II)**77**, Cu(II)**78**, Zn(II)**79**, and Cd(II)**80** complexes. The copper complex exhibited the highest level of activity, and it was determined that a concentration of 46 µg/ml was required for 50% mortality. The free ligand displayed almost no cytotoxic activity. In mice having Ascites tumors, administration of the copper complex**78** at varying doses (10, 5, and 1 mg/kg b. wt) exhibited an inhibitory effect on the formation of solid tumors and a concentration-dependent improvement in the mean survival rate and life duration. The copper complex**78** of acetoacetanilide N(4)-methyl(phenyl)thiosemicarbazone (AcTSC) has been shown to have cytotoxic and antitumor effects in vitro, which implies that it may find application as an anticancer agent [60].

Two novel classes of nickel and zinc complexes comprising ONS donor sets of the 1-(2-hydroxy-3,5-diiodobenzylidene)-4-phenylthiosemicarbazide ligands have been synthesized by Kumar, S. Mathan, et al. and they are characterized using X-ray crystallographic, IR, ^1H NMR, and UV spectral data. Thiosemicarbazone complexes

have a square planar shape, with deprotonated ligand molecules acting as binegative and tridentate chelators. According to X-ray crystallographic data complex **81** has a square planar structure, while complex **82** possesses a trigonal bipyramidal distorted square pyramidal structure. The synthesized ligand is examined for its cytotoxic effect against human breast cancer cell lines in comparison to its complexes. According to the preliminary biological assays, both complexes and the free ligand have inhibitory effects on human adenocarcinoma cancer cell lines. Moreover, the activity findings indicate that the thiosemicarbazone has greater potency against the MCF-7 cancer cell line compared to complexes **81** and **82**. The stability of the compound and the critical biological role of the phenylthiosemicarbazone ligand justifies broadening the research attention [61].

Three tridentate Schiff bases were obtained by Mokhtaruddin, Nur ShuhadaMohd, et al. reacting S-2-methylbenzyldithiocarbazate, 4-methyl-3-thiosemicarbazide, and 4-ethyl-3-thiosemicarbazide with 2-acetylpyridine and 2-acetyl-4-methylpyridine. These groups of three compounds then reacted with Cu(II) saccharinate, resulting in three new mixed-ligand Cu(II) saccharinate complexes**83a** and **83b**. Following their synthesis, three novel mixed-ligand and binuclear copper(II) complexes with general formula was [Cu(sac)(L)]2 (sac = saccharinate anion; L = anion of the Schiff base were identified using IR and UV/Vis spectroscopy, molar conductivity, and magnetic susceptibility measurements. Using the pyridyl-nitrogen, azomethine-nitrogen, and thiolate-sulphur atoms as points of coordination, the Schiff bases exhibited tridentate NNS donor ligand behavior, according to the spectroscopic results. Owing to the conductivity measurements and the magnetic data, the complexes were largely non-electrolytes in DMSO and were found in a square pyramidal framework. Examination of all of the complexes to the Schiff bases alone revealed that they were more cytotoxic against MCF-7 and MDA-MB-231 cancer cells. This was hypothesised to be caused by a number of elements, including the planarity of the complexes, the chelation effect, and the fact that compounds formed by metal ions attached to multidonor chelating ligands are more lipophilic, making it simpler for the compounds to enter cancer cells [62].

Spectrometric analysis, UV-visible, FT-IR, and NMR spectroscopy were used by Mathews, Nimya Ann, et al. to describe the Cu(II) and Zn(II) complexes that they obtained from a thiosemicarbazone derivative (H_2esct), together with their respective metal acetates and 2,2'-bipyridine as the base. The complexesare monomeric in nature, as demonstrated by X-ray diffraction investigations, and they bind to the thiosemicarbazone derivative in a tridentate dideprotonated form. Different kinds of intermolecular interactions were seen in the crystal structures of the complexes, and these interactions were further examined using fingerprint plots and Hirshfeld surface analysis. The importance of hydrogen bonds and weak non-covalent forces in the formation of supramolecular structures is amply supported by the current investigation. The conductivity measurement studies demonstrated that the metal

complexes were not electrolytic. The cytotoxicity of Cu(II) **84** and Zn(II)**85** complexes against Dalton lymphoma ascites cell lines in vitro was demonstrated to be greater than that of their respective proligands [63].

When pyridine-2-carbaldehyde, quinoline-2-carbaldehyde, 2-acetylpyridine, 2-acetylquinoline, or equivalent 2-pyridyl ketones were condensed with thiosemicarbazides $RNHC(S)NHNH_2$ and $R=CH_3$, C_6H_5, ten thiosemicarbazone ligands were synthesized by Schulz, Ellina, et al. in a good amount of yield. The reaction between $[PdCl_2(cod)]$ and either cod=1,5-cyclooctadiene or $K_2[PtCl_4]$ produced Pd(II)**86a-e**, **88a-b**and Pt(II)**87a-j**, **89a-b**complexes that were separated with high purity, as confirmed by ^1H, ^{13}C, and, when appropriate, ^{195}Pt NMR spectroscopy in combination with CHNS analysis. Four human glioblastoma cell lines were used to test the cytotoxicity of the synthesized compounds. The most active complex had an EC_{50} value of 2.1 μM and was significantly more active than cisplatin despite having a Pd(II) center. The EC_{50} values showed an unexpected negative correlation with lipophilicity and a decrease with alkyl substituent length (C1>C8>C10). The Pd(II) complexes**86a-e**and **88a-b**are substantially more effective than their Pt(II) **87a-j** and **89a-b**equivalents, according to correlation with the various structural motifs, and the most promising anticancer activity is associated with a maximum of two aromatic rings plus one methyl group [64].

Antibacterial/Antifungal/Anti-inflammatory Properties

syntheses and characterization of some new Ni(II) complexes**90a-f** of 4-(p-X-phenyl)thiosemicarbazones of salicylaldehyde were described by Saswati et.al. The inductive effect of the substituent X (X = F, Br and OCH_3), in order to observe its influence, if any, on the redox potentials and biological activity of the complexes was studied. this paper reveals that the structural parameters (e.g. Ni–N and Ni–P bond distances) and the redox potentials of these complexes can be fine-tuned by changing the substituent on the 4-aryl (X) part. The molecular structures of four mononuclear (**90a-c** and **90e**) and one dinuclear**90f**Ni(II) complex have been determined by X-ray crystallography. The complexes were screened for their antibacterial activity against Escherichia coli and Bacillus. The minimum inhibitory concentrations of these complexes and their antibacterial activities indicate that compound **90d** is the potential lead molecule for drug designing [65].

Ni(II) with p-[N,N-bis(2-chloroethyl)amino]benzaldehyde-4-methyl thiosemicarbazone (CEAB-4-MTSC) were synthesized and characterized by elemental analysis and spectrochemical method by AnithaSankaraperumal and team. The crystal structure of the free ligand and complex**91** was determined by single crystal X-ray diffraction technique, the complex crystallizes in the triclinic with space group P. In the complex, thiosemicarbazone ligand is coordinated to nickel via SNNS mode. In the crystal, molecules are linked through intermolecular C-H----Cl hydrogen bond network, generate edge fused ring motif that stabilizes the crystal structure. The complex**91** was tested for their antibacterial activity against various pathogenic bacteria. From this study, it was found out that the activity of complex reaches the effectiveness of the conventional bacteriocide Streptomycin compared to simple ligand [66].

Using 2-Acetylpyridine-N(4)-cyclohexylthiosemicarbazoneligand Salam, M. A., et al. prepared their organotin(IV) complexes **92a–e**, and performed a detailed investigation of the compounds by different spectroanalytical methods. According to single crystal X-ray diffraction analyses, the tin complex [$PhSnCl_2$(APCT)] **92d** was six-coordinated and exceptionally adopts an distorted octahedral structure in which the coordination occurs through the ligand's pyridine-N, azomethine-N, and thiolato-S atoms. With the space group P21/n, the compound crystallizes as a monoclinic lattice. Using doxycycline as the reference drugs, the antibacterial activities of synthesized ligand (1) and its organotin (IV) complexes **92a–e**were determined. According to the screening results, the free ligand has less bactericidal activity than the organotin(IV) complexes. With 27.6, 27.5, 25.9, and 24.8 mm inhibition zones against S. aureus, E. coli, E. aerogenes, and Salmonella typhi, respectively, diphenyltin(IV) complex **92e** demonstrated the greatest prevention of organism development. Based on biological investigations, the diphenyltin(IV) complex **92e** is more active than the other organotin(IV) derivatives, but all of the organotin(IV) complexeshave more potent antimicrobial properties than their free ligand. The findings support earlier reports on tin compounds, which have been shown to have enhanced activity as a result of ligand-metal coordination and effective metal complex migration into bacterial cells [67].

Aljahdali, Mutlaq Shedeed, Yahia Hassan Elmalik, and Gaber Mohamed Abu El-Reash presented four novel mixed ligand metal (II) complexes**93-96** with 1,10-phenanthroline and 1-methylpyrazole, 3-aldehyde, and 4-(2-pyridyl)thiosemicarbazone (MPAPT). Elemental analysis, spectroscopic techniques IR, ^{1}HNMR, and UV-Vis and magnetic moment measurements were used to describe these complexes. Octahedral structures were assigned to all complexes based on spectral and magnetic moments data. With the help of the azomethine, pyridine, and thiolate sulfur atoms following deprotonation, the thiosemicarbazone ligand coordinates to the metal(II) ion in these complexes as a tridentate anion while, through the two nitrogen atoms in pyridine, 1,10-phen is coordinated as a neutral bidentate ligand. The results of the antifungal and antibacterial screening indicated that recently developed compounds have the potential to be antimicrobial agents. Cu(II) complex**94** exhibited more anticancer activity in comparison to carcinoma of the larynx [68].

The Complexes of copper(II)**97a-d**, vanadium(V)**98** and nickel(II)**99** with 1-phenyl-3-methyl-4-benzoyl-5-pyrazolone 4-ethyl-thiosemicarbazone (HL) were synthesized by Pahontu, Elena, et al. and characterized using elemental analyses, IR, ^{1}HNMR and ^{13}CNMR spectroscopy. An analysis of the IR spectra reveals that the ligand is tridentate. Single-crystal X-ray diffraction has been used to determine the structures of the ligand and its complexes with vanadium(V) and copper(II). The Cu was found in tetrahedral, square planar and distorted square pyramidal geometry in its complexes**97a-d**. Various physicochemical approaches, including molar conductivity, magnetic susceptibility tests, and electronic, infrared, and electron paramagnetic resonance spectral examinations, have been used to analyze the copper(II)**97a-d**, vanadium(V)**98**, and nickel(II) complexes**99**. According to the antimicrobial data provided for the compounds in this article, metal complexes typically exhibit greater activity than free ligands. When compared to cells harbouring inner sphere halogen, the copper complexes, which include the tridentate O,N,S ligand, have a significant antiproliferative action for HL-60 leukaemia cells. Of the compounds in the series, complex **97b**, which is encapsulated with two ligands, exhibits the strongest antiproliferative effect [69].

Several novel complexes of zinc(II)**100a-h** with 5-nitro-salicylaldehyde-N1-substituted thiosemicarbazones have been created by Indoria, Shikha, et al. utilizing bipyridines/phenanthrolines as co-ligands. These complexes have been characterized by elemental analysis, infrared, NMR, electronic absorption and fluorescence spectrocopy, and single crystal X-ray crystallography. Zinc(II) complexes containing 5-nitro-salicylaldehyde-N1-substituted thiosemicarbazones exhibited in distorted trigonal bipyramidal geometry, distorted square pyramidal geometry, and geometry intermediate between square pyramidal and trigonal bipyramidal shape. Significant antibacterial action against methicillin-resistant Staphylococcus aureus (MRSA), Klebsiella pneumoniae (MTCC109), Shigella flexneri (MTCC1457), Selmonella typhimurium (MTCC741), Candida albicans (MTCC227), and Staphylococcus aureus (MTCC740) has been demonstrated by these zinc(II) complexes. Every compound exhibits activity against K. pneumoniae and S. typhimurium, whereas complexes documented in literature have been found to be inactive. The zinc(II) complexes**100a-h** exhibited remarkable efficacy against the resistant bacterial strain Sh. flexneri; however, no literature report has been found for purposes of comparison. The addition of bipy and phen co-ligands, which have a greater ability to enter cell membranes, may improve the lipophilicity of these complexes, which in turn may boost their antimicrobial activity. This study significantly advances the utilization of zinc(II) thiosemicarbazone complexes, which have not before been documented to be effective antibacterial agents for this family of ligands [70].

The ONS donor ligand, 1-phenyl-3-methyl-4-benzoyl-5-pyrazolone, and N(4)-methyl-N(4)-phenylthiosemicarbazone (H_2L) were synthesized and characterized by Sangeetha, K. G., and K. K. Aravindakshan using spectrochemical tools. According to the study, the coordination capacities of trimemacarbazones are uncertain and it has been shown that the same ligand has coordinated in various ways with different salts of the same metal. The diamagnetic square planar complex, $M(HL)CH_3COO$, was produced by nickel acetate**101a**, however, the paramagnetic octahedral complex, $M(HL)_2.H_2O$, was produced by nickel chloride**101b**. The diamagnetic Cu(II) complex firmly verifies that it exists as a dimer in the solid state. Additionally, the ligand, copper, and zinc complexes underwent an initial in vitro antibacterial screening. Four fungal strains and three Gram (+ve) and Gram (–ve) bacterial strains were employed in this study. In comparison to the ligand, complexes exhibited superior microbial inhibitory activity. Additional research will be required to elucidate the findings of this experiment, which indicated that the compounds had a particular effect on microorganisms [71].

A complete synthesis and characterization, including an X-ray diffraction analysis of the methoxy-containing benzodiazaborine by Scott, Ryan S., et al., has been accomplished for two new thiosemicarbazones and three new benzodiazaborines generated from 4-ethyl-3-thiosemicarbazide. However, it was found that the thiosemicarbazones **105b** and **105c**, which included boron, were not effective palladium ligands due to the cleavage of the boron group in interactions with palladium(II) acetate in THF and EtOH. Every compound was tested for its antifungal and antibacterial properties against two different types of fungi: Aspergillus niger and Saccharomyces cerevisiae; two different types of bacteria: Bacillus cereus (Gram-positive) and Pseudomonas aeruginosa (Gramnegative). Compounds **104a**, **105a** and**105b**, shown notable efficacy against Saccharomyces cerevisiae [72].

Kotian, Avinash, et al synthesized and analyzed three possible metal ion chelating ligands, p-halo N4-phenyl substituted thiosemicarbazones (E)-4-(4-halophenyl)-1-(3-hydroxyiminobutan-2-ylidene). The molecular structure of all three thiosemicarbazones were also determined using the single crystal X-ray diffraction technique. From these ligands, a number of Co(III)**106** and Ni(II)**107** mononuclear transition metal complexes have been produced and characterized using a variety of spectro-analytical techniques. Every ligand has formed in a monoclinic crystal system with a $P2_1/n$ space group, based on the crystal structures. Through $R_2^2(8)$, $R_2^2(12)$, and $R_2^2(14)$ ring motifs, the ligands exhibit C—H···S and N—H···S intermolecular interactions, which are responsible for forming supramolecular self-assemblies. The antibacterial properties of the produced compounds have been studied in vitro. It is discovered that the compounds are more effective against E. Coli and A. niger than the standard employed. Compounds are also studied for their in vitro antitubercular efficacy as well. The complexes exhibit hyperactivity against Escherichia coli and Aspergillus niger, according to antibacterial data. In comparison to the usual medication, ciprofloxacin, L1 is ten times and its complexes five times more potent, and its ligands are twenty times more active than fluconazole. These findings demonstrate how cobalt(III)**106** and nickel(II) **107**complexes may be used to produce chemotherapeutic drugs that block the action of microorganisms [73].

The coordination property of the novel N4-morpholinyl isatin-3-thiosemicarbazone (HL) toward Co(II)**108**, Cu(II) **109a-d**, Pd(II)**110**, Ni(II)**111** andZn(II)**112** has been investigated, and El-Sawaf, Ayman K., et al. outlined the complex structures using physico-chemical techniques. Spectroanalytical studies suggest that the ligand forms two five-membered rings with cobalt, copper, and palladium and forms complexes of the kind [M(L)X], where M is either Co, Cu, or Pd and X is either Cl, Br, or OAc. In contrast, the ligand bonded to $ZnCl_2$ as a neutral bidentate NS donor and to $NiCl_2$ as a neutral tridentate ONS donor. It was determined that, with the exception of the Ni(II) complex**111**, which has a tendency to have a square pyramid structure, all complexes formed square planar geometries as a result of the Schiff base ligand coordinating through the oxygen, nitrogen, and sulfur atoms of the C=O, C=N, and C=S groups to the metal ions. The antibacterial and antifungal properties of thiosemicarbazone and its metal chloride and bromide complexes have been investigated. Because of coordination and chelation, metal complexes function as more effective and regulating antimicrobial agents, which inhibit the growth of bacteria. In comparison to free thiosemicarbazone and all other complexes, $[Cu(L)Br]_0.5H_2O$, complex **109b**exhibits stronger biological activity, according to the results of experiments [74].

By condensation of the substituted isatin molecule with N(4)-phenyl-3-thiosemicarbazide, Munikumari, Gandham, et al. are able to produce substituted heterocyclic (isatin) attached thiosemicarbazone ligands (L_1–L_3) in good yields. Analysis and characterization of the compounds have been conducted using both spectroscopic and analytical approaches. The complexes **113a-c** may be speculatively presented as square planar geometry around Pd based on the spectral data. According to the findings of the antimicrobial activity tests, complexes **113a** and **113b** exhibited strong antibacterial activity against K. pneumoniae and B. subtilis, while complex **113b** also shown good antifungal activity against the microorganisms. The antioxidant activity of the compounds was examined, and the findings indicated that complex **113c** exhibited superior antioxidant properties with IC_{50} values of 7.24 ± 0.09 mM when compared to conventional ascorbic acid. Furthermore, complex **113c** demonstrated significant activity against HeLa cell line in comparison to the standard, with an IC_{50} value of 16.52±1.08 mM, according to the in vitro antiproliferative activity studies. The outcomes of the molecular docking investigations indicate that complex **113c** binds to the EGFR target receptor with minimal binding energies of about 8.08 kcal mol^{-1} [75].

Employing analytical and physico-chemical analysis, Rusnac, Roman, et al. verified the composition of the four newly isolated coordination Cu (II) compounds**114c-d** containing two thiosemicarbazones tridentate bibasic ligands. The obtained single crystals were examined using X-ray diffraction to ascertain their structures; in the case of H2L1, Cu(II) **114a-b**has a square-planar geometry, while in the case of H2L2, Cu(II) **114c-d**has a square pyramidal core. Only the solvent from the outer sphere varies in the coordination compounds [Cu(HL1)Cl]C_2H_5OH **114a**and [Cu(HL1)Cl]DMF, which share the identical set of coordinating atoms through the atoms of enolic oxygen, aomethine nitrogen, and thionic sulfur at the central atom. The best antibacterial activity is found in [$Cu_2(HL2)_2Br_2$]DMF**114d**, with a MIC of 0.031 mg/mL, while the antiproliferative activity of [Cu(HL1)Cl]C_2H_5OH**114a**, [Cu(HL1)Br]C_2H_5OH**114b**, and H2L1 against HEp-2, BxPC-3, RD, and L20B is modest [76].

A number of cis-dioxomolybdenum(VI) complexes**115a-h** have been synthesized by ElenSenol, et al. using novel thiosemicarbazone compounds that include substituents on both the amidic nitrogen and sulfur, with solvent molecules offering extra coordination. Compounds are investigated using elemental analysis, IR and ^{1}H NMR spectroscopies. X-ray single-crystal diffraction was used to determine cis-dioxo-(3-ethoxy-2-hydroxybenzaldehyde-N-ethyl-S-methyl-thiosemicarbazonato-(N,N',O)-methanol-molybdenum(VI) **115e**. In addition, the complexes were evaluated against bacterial and fungal strains, including S. Aureus, P. Aureginosa, E. Coli, and C. albicans. The outcomes were compared to those of standard antibacterial drugs. The compounds that were evaluated showed that L^{1}, **115f**, **115b**, and **115a** exhibited the strongest antifungal activity against Candida albicans, whereas L^{3}, **115e**, and **115f** shown the strongest antibacterial activity against E. coli, P. aeruginosa, and S. aureus [77].

Damit, NurinSakinatulHayati Haji, et al. synthesized and structurally characterized many metal complexes of the formulas $[Zn(NNS)_2]$**116**, $[Ni(NNS)_2]$**117**, $[Cd(NNS)_2)]$**118**, $[PbHNNS(NO_3)_2]$**119** and [Cu(NNS)]**120** and using a range of physico-chemical methods. The lead(II) ion is coordinated to the thiosemicarbazone ligand as an uninegatively charged bidentate NS chelating agent via the azomethine nitrogen atom and the thiolate sulfur atom in the mono-ligated nitrato-complex, which has a distorted square pyramidal shape. The bis-ligand zinc(II) complex**116** $[Zn(NNS)_2]$ has two uninegatively charged tridentate NNS thiosemicarbazone ligands that coordinate through one of the nitrogen atoms in quinidine, one of the nitrogen atoms in azomethine, and one of the sulfur atoms in mercaptide. The zinc atom in this complex assumes a distorted octahedral geometry around the zinc (II) ion. Evaluation of antibacterial investigations of these compounds revealed that, in comparison to the HNNS ligand, $[Cu(NNS)NO_3]$**120**, $[Zn(NNS)_2]$**116**, and $[Cd(NNS)_2]$ **118** exhibited higher inhibitory action. $Ni(NNS)_2$ did not exhibit any inhibition, while $[PbHNNS(NO_3)_2]$ **119** only shown a little inhibition [78].

Researchers Ali, Mayada S., and Mohamad Hasan have examined the ability of (2E,2 } E)-2,2 } -(pyridine-2,6-diylbis(ethan-1-yl-1-ylidene))bis(N-ethylhydrazine-carbothioamide), H_2L to chelate the ions VO^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Pd^{2+}, Pt^{2+}, and Cu^{2+} (Cl^-or ClO_4^-) both separately and in combination (Cu^{2+}/Ag^+). The ligand exhibits an orthorhombic crystal structure, and molar conductivity values distinguish the complexes as conducting [Co^{2+}, Ni^{2+}, Mn^{2+}, $Cu(ClO_4)_2$ and Cu^{2+}/Ag^+] or nonconducting. The ligand chelates in several modes, including neutral and dibasic pentadentate (N_3S_2) and neutral and dibasic tetradentate (N_2S_2). The Co^{2+}**122**, Ni^{2+}**123**, and Zn^{2+}**124** complexes support mononuclear complexes, whereas the others support binuclear complexes, with the exception of Pd^{2+}**127**, which revealed a trinuclear complex. The Co^{2+} and Ni^{2+} complexes are speculated to have an octahedral structure, whereas the Cu^{2+}**125** and Mn^{2+}**126** complexes are presented as square pyramids. The synthesized compounds were examined for antibacterial action, and the VO^{2+}**121** complex was the most impressive of all complexes, with the maximum activity on Bacillus and a low activity on E.coli [79].

$VOSO_4.H_2O$

Shawish, Hana Bashir, et al. prepared Ni(II) complexes with N4-substituted thiosemicarbazones and studied its potential anti-inflammatory activity. Synthesis and characterization were carried out for four ligandsand the corresponding complexes **131a-d**containing nickel. The effects of the synthesized compounds on pro-inflammatory cytokine production, NF-kB transactivation activity, and NF-kB nuclear translocation were examined. By using molecular docking studies, an additional binding site for the active drug was also predicted. Out of all the synthetic compounds that were examined, complex $[Ni(H_2L^1)(PPh_3)]Cl$ **131a**was shown to be highly effective in inhibiting the degradation of IkBα and the nuclear translocation of NF-kB p65 in both LPS-stimulated RAW264.7 cells and TNFα-stimulated HeLa S3 cells. Furthermore, complex **131a** substantially suppressed the transcription of NF-kB

target genes, including those encoding the pro-inflammatory cytokines TNFa, IFNb, and IL6, that is stimulated by LPS or TNFα. Furthermore, complex 5's suppressive impact on the development of carrageenan-induced paw edema in wild type C57BL/6 mice provided additional evidence for its anti-inflammatory properties. It's interesting to note that a molecular docking research suggested complex **131a** could have an interaction with IKKb's active site. When considered collectively, it is proposed that complex **131a**as a new inhibitor of NF-kB with strong anti-inflammatory properties [80].

AnticancerProperties

Pathan, Aishakhanam H., et al. have synthesized ethyl 2-(2-(4-chlorophenylcarbamothioyl)hydrazono)propanoate, a chelating agent containing S,N,O donor sites, specifically for the synthesis of Cu(II) **132**, Co(II)**133**, Ni(II)**134**, and Zn(II)**135** complexes. In connection with Cu(II), Co(II), Ni(II), and Zn(II) ions, the ligand LH functions as a tridentate monobasic chelate, resulting in octahedral arrangements. When compared to the ligand and other complexes, the copper complex**132** has demonstrated redox reactions within the applied voltage range. In vitro antiproliferative activity of the newly synthesized complexes against human cancer cells of various origins, including COLO-205 and K-562, has been assessed. The IC_{50} value of the copper complex**132** among the substances examined for their antiproliferative activities is 15.16 and 8.65 lM for K-562 and COLO-205, respectively. CuL had strong antiproliferative activity among the complexes examined, with its efficacy being on par with that of the common medication cisplatin. CuL mostly inhibited cell growth by inducing apoptosis, as demonstrated by the accumulation of sub G0/G1 cells in flow cytometry and confocal imaging. A higher concentration of nucleophilic sites (H_2O) appears to impact the complex's overall biological activity significantly. Redox active Cu and the presence of water have specifically increased biological activity [81].

A number of copper (II) benzoylpyridine thiosemicarbazone complexes**136a-f** were synthesized and studied by Casas, J. S., et al. Following their NMR, MS, and melting point characterization, these mono-anionic tridentate ligands were combined with Cu^{2+} to produce the novel square planar metal complexes [Cu(BZP-tBTSC)Cl] **136c** and [Cu(BZP-BzTSC)Cl]**136d**. Human topoisomerase IIα is significantly inhibited by all of the copper complexes. When it comes to human breast cancer cell lines, the [Cu(BZP-tBTSC)Cl]**136c** complex has significant activity. The effectiveness of copper(II) complexes in inhibiting the action of human topoIIα does not appear to be significantly impacted by the alkyl and aryl substituents on the end of the thiosemicarbazone ligand, such as methyl, ethyl, tert-butyl, phenyl, etc. The inhibition of topo-IIα by the copper complexes appears to be mediated by their square-planar geometry, which is uncommon for copper (II), as well as the characteristics of the Cu-Cl bond. The findings indicate that the [Cu(II) BZP-TSC] complexes exhibit superior topo-IIα inhibition compared to the BZP-TSC ligands. While, the [Cu(BZP-tBTSC)Cl]**136c** complex demonstrates dose-dependent topo-IIα inhibition [82].

The authors Gatti, Anna, and coworkers synthesized two new half-sandwich complexes, one containing a thiosemicarbazone ligand (L) and the other containing osmium (II)**137a-b**and ruthenium (II)**138a-b**. The compounds were characterized using a variety of spectrometric techniques, and their structures were determined through single crystal X-ray crystallographic analysis. All the complexes, as revealed by X-ray crystallography, have half-sandwich pseudo-octahedral "three-legged piano-stool" structures, where a terminal chloride and a neutral N,S-chelating thiosemicarbazone ligand occupy three coordination sites. It was found that the coordinated thiosemicarbazone ligand underwent E/Z isomerization in methanol, partial dissociation in an aprotic solvent (acetone), and total displacement in a more coordinating solvent (DMSO). Positive outcomes were observed, especially with regard to HCT116 colon cancer cells, where the metal complexes exhibit potencies up to 20 times greater than those of the equivalent free ligand L_2. As evidenced by the findings for A2780 ovarian cancer cells and its derived CDDP-resistant cell line A2780Cis, ruthenium complex (3) has remarkable anticancer properties and the potential to overcome CDDP resistance. All the complexes had resistance factors that were lower than those of the therapeutic medication cisplatin. In the future, efforts will be focused on refining the pharmacological characteristics of these complexes, particularly with regard to stability in biological testing scenarios [83].

Anjum, Rukhsana, et al. synthesized and characterized a series of eight bis(thiosemicarbazone) ligands and 16 copper (II) and zinc (II) complexes with varying substituents at the diimine position. Zn(II) complexes Zn($ATSM_2$)(DMSO)**140a**, Zn($PyTSM_2$)(DMSO)**140d**, and Zn-($PGTSM_2$)(H_2O)**140g** exhibited a distorted square pyramidal geometry, whereas Cu(II) complexes Cu($GTSM_2$)**139b**, Cu(GTSCM)**139c**, Cu-($PyTSM_2$)**139d**, Cu($EMTSM_2$)**139f**, and Cu($PGTSM_2$)**139g** displayed a distorted square planar geometry. By thoroughly examining their physical and biological characteristics, they were able to ascertain the structure-activity connections of these drugs. In this regard, it was crucial to remember that in order to optimize the antiproliferative action of this class of ligands, the diimine backbone must remain unsubstituted. The Cu(II) or Zn(II) complexes of the ligands did not exhibit a significant correlation with their activity. Most of the bis(thiosemicarbazones) Zn(II) complexes**140a-h** were not as active as their corresponding ligands. Cu(II) diacetyl bis(4,4-dimethyl-3-thiosemicarbazone) [Cu($ATSM_2$)]**139a** and Cu(II) glyoxal bis(4,4-dimethyl-3-thiosemicarbazone) [Cu($GTSM_2$)]**139b** showed the strongest antiproliferative effect against tumor cells among all the agents. Their antiproliferative action was significantly reduced by substituting hydrophobic moieties at the terminal N atom and the diimine site. Surprisingly, relative to normoxic growth conditions, hypoxia that is found in the tumor microenvironment decreased the antiproliferative efficacy of most bis(thiosemicarbazones) and their copper complexes. It was noteworthy that the antiproliferative activity of the majority of is (thiosemicarbazones) and their Cu(II) complexes was diminished by hypoxia [84].

A group of copper(II) complexes**141a-f** with different substitutions for the salicylaldehyde thiosemicarbazone ligand were synthesized and their activities shown by Carcelli, Mauro, et al. A panel of cell lines (HCT-15, LoVo and LoVo oxaliplatin resistant colon carcinoma, A375 melanoma, BxPC3 and PSN1 pancreatic adenocarcinoma, BCPAP thyroid carcinoma, 2008 ovarian carcinoma, HEK293 nontransformed embryonic kidney) was used to evaluate the in vitro activity of both ligands and copper complexes. The results showed that the metal complexes had remarkable activity, sometimes in the low nanomolar range. With regard to human pancreatic (BxPC3 and PSN1) and colon (HCT-15) cancer cells, the most potent copper(II) complex **141a** was about 466, 1510, and 3480 times more successful than cisplatin. It was also 60 times more active than cisplatin in 3D spheroids of HCT-15 and PSN1 cancer cells. The ability of the copper(II) complexes to potently block Protein Disulfide Isomerase, a copper-binding protein that has recently emerged as a new therapeutic target for cancer treatment. These metal-based compounds appear to be a highly promising weapon in the battle against cancer, based on positive preliminary results in C57BL mice [85].

Anitha, Panneerselvam, et al. have synthesized and studied the novel ruthenium(II) complexes of type $[RuCl(CO)(EPh_3)(L)]$ where E = P or As and L = monobasic tridentate ONS/ONO ligand, using analytical and spectroscopic techniques such as FT-IR, electronic, ^{1}H, ^{13}C, ^{31}P NMR, and ESI–MS etc. Through quinone oxygen, imine nitrogen, and thiolato sulfur/enolate oxygen, the ligands were coordinated to ruthenium. The octahedral environment surrounding the ruthenium(II) ion was shown by the pattern of the electronic spectra of all the complexes, which was consistent with previous ruthenium complexes. The compounds were evaluated for their potential to inhibit tumor growth in different cancer cell lines and for their drug-like characteristics, including DNA binding, DNA cleavage, and radical scavenging ability. A thorough analysis of the DNA-binding characteristics of complexes **142a-d** was conducted using a variety of techniques, such as electronic absorption spectroscopy, EB displacement, viscosity, and thermal denaturation tests. At ambient temperature, the apparent binding constant value (Kb) of complex **142c** was predicted to be 2.27 X 10-3 M-1 based on DNA binding tests that showed ruthenium(II) complexes may interact with DNA by non-intercalation. The existence of various modifications on the terminal portion of the thiosemicarbazone moiety can convincingly account for the trend in the DNA-binding affinities of this series of complexes. The results of the DNA cleavage studies indicate that the complexes exhibit superior pBR 322 DNA cleavage properties. The significant radical scavenging ability of the complexes against free radicals was demonstrated by their antioxidant activity. The results of the cytotoxic activities revealed that the ruthenium(II) complexes had a greater ability to kill specific cancer cells [86].

Neutral and cationic copper bis(thiosemicarbazone) complexes**143a-g** bearing methyl, phenyl and hydrogen, on the diketo-backbone of the ligands were synthesized and characterized by spectroscopic and X-ray crystallographic methods by DuraippandiPalanimuthu and associates. Their in vitro cytotoxicity studies revealed that they are cytotoxic unlike the corresponding zinc complexes. Copper complexes Cu(GTSC)**143f** and Cu(GTSCHCl) **143c**derived from glyoxal-bis(4-methyl-4-phenyl-3-thiosemicarbazone) abbreviated as $GTSCH_2$ were found most cytotoxic complexes against various human cancer cell lines, with a potency similar to that of the anticancer drug adriamycin and up to 1000 fold higher than that of the corresponding zinc complex. Tritiated thymidine incorporation assay revealed that Cu(GTSC)**143f** and Cu(GTSCHCl) **143c**inhibit DNA synthesis substantially. Complex Cu(GTSCHCl) caused distinct DNA cleavage and Topo IIα inhibition unlike Cu(GTSC). In vivo administration of Cu(GTSC) significantly inhibits tumor growth in HCT116 xenografts in nude mice [87].

The synthesis, characterization, DNA interaction studies, in vitro cytotoxicity, and inhibitory activity evaluation of four cationic compounds**144a-d** of the type [PdX(PPh_3)(4-MeT)]X {PPh_3 = triphenylphosphine; 4-MeT = 4-methyl-3-thiosemicarbazide; X = Cl**144a**, Br**144b**, I**144c**, SCN**144d**} were presented in this work by Rocha, Fillipe V., et al. Using elemental analysis, IR and ^{1}H NMR spectroscopies, and ESI/MS spectra, the synthesis of the [PdX(4-MeT)(PPh_3)]X compounds was verified. With bond lengths and angles falling within the standard range, the palladium atom takes on a distorted square-planar geometry. A five-membered ring is formed through cis coordination between the S1 and N2 atoms of thiosemicarbazide, which functions as a neutral bidentate ligand. A triphenylphosphine ligand coordinated trans to N2 and an iodide ion **144c** or thiocyanate group **144d** occupy the other two coordination sites of the palladium atom. Using the colorimetric MTT test, the in vitro cytotoxic activity of ligand 4-MeT and complexes **144a-d** was assessed against the murine mammary adenocarcinoma (LM3), lung adenocarcinoma (LP07), and human breast cancer (MCF-7) cell lines. According to experimental results using the LM3 cell line, all Pd(II) compounds demonstrate cytotoxicity greater than that of cisplatin, with IC_{50} values ranging from 3.22 to 6.05 μM. The complexeswere approximately five times more effective than etoposide against MCF-7 tumor cells, exhibiting impressive cytotoxic levels spanning the 7.66–11.03 μM dose range. Complexes have been tested for their ability to block topo I and IIα activity by incubating topo with circular plasmideal DNA pBR320 in a concentration-dependent manner. The present investigation led to the hypothesis that these complexes might function as catalytic inhibitors of topo II, vying with ATP for the ATPase domain [88].

Türkkan, Ercan, and colleagues synthesized novel copper complexes of 2-hydroxy-5-methoxyacetophenone thiosemicarbazone and its N(4)-substituted derivatives. The compounds were characterized through theoretical DFT analyses and experimental measurements of conductivity, magnetic susceptibility, UV-Vis, FT-IR, and EPR spectral analysis. The EPR, UV-Vis, and DFT examinations, as well as the derived bonding characteristics, demonstrate that all of the complexes have square planar geometry, and their M-L bonds have strong ionic and in-plane σ-bond character. The geometric parameter G ranges from 7.61 to 7.86 for all compounds, indicating their mononuclear nature. When the Cu(II) complexes**145a-c** under investigation were examined for biological activity, they demonstrated both in vitro antibacterial and anticancer activities. The complexes demonstrated antibacterial properties against S. aureus, a Gram-positive pathogen, but showed no action against S. gallinarum and E. coli, two Gram negative bacteria. The cytotoxicity experiments indicate that these complexes exhibit strong cytotoxic activity against the chemoresistant MDA-MB-231 cell line. Notably, Cu(HMAET)Cl **145b**in particular may be evaluated as a novel therapeutic approach to address multidrug resistance in cancer therapy. These copper compounds may have anticancer properties that could help combat the pharmaceutical resistance of cancer cells that have spread to other locations [89].

Mahendiran, Dharmasivam, et al. synthesized and studied six novel bis(thiosemicarbazone)copper(I) complexes **146a-f** of the type $[Cu(L^{1\text{-}6})_2Cl]$. By means of two thione sulfur atoms from two ligand molecules and one chloride ion, the complexes exhibited a trigonal planar 'Y' shaped geometry. Spectral and molecular docking experiments show that all of the complexes intercalatively bond with calf thymus DNA (CT-DNA). Through static quenching mode, the complexes interact with BSA in an efficient manner. Via electrostatic, van der Waals, hydrogen bonding, π-π, and σ- π interactions, all of the complexes have a robust interaction with the epidermal growth factor receptor. By using the MTT assay in conjunction with cisplatin, in vitro antiproliferative activity of the complex was evaluated against two normal (NHDF and L6 myotubes) and four malignant (MCF-7, HeLa, Hep-2, and EAC) cell lines. In comparison to other evaluated cell lines, all of the complexes efficiently kill the EAC tumour cell line. The complexes appear to have triggered apoptosis in EAC cancer cells based on elevated ROS production, apoptotic, and cell cycle studies. Cellular uptake investigations demonstrated that the complexes can enter the cytoplasm and accumulate in cell nuclei. In addition, it was discovered that complexes **146b** and **146c** suppressed the growth of Ehrlich ascites carcinoma (EAC) tumor cells in vivo using a model of female Swiss albino mice [90].

Schiff base metal complexes with the formulations $[Ni(L1)_2]$ **147a**, $[Ni(L2)_2]$ **147b**, and $[Ni(L3)_2]$ **147c** of the ligands (L1=fluorene-2-carboxaldehyde thiosemicarbazone, L2=fluorene-2-carboxaldehyde–4-methyl–thiosemicarbazone, and L3=fluorene-2-carboxaldehyde–4-ethyl–thiosemicarbazone) have been synthesized and analyzed by Savir, Savina, et al. The findings suggested that the thiosemicarbazone ligands acted as bidentate ligands, with their N and S atoms serving as a coordination bridge to the Ni(II) ion. Two of the six compounds that were examined, complexes 5 and 6, showed modest in vitro antimalarial activity, with respective IC50 values of

23.79 and 2.29 mM. The cytotoxic and antimalarial properties of the N(3) substituent are portrayed by its characteristic. The molecular weight and hydrophobicity of the substances under consideration are two important factors to take into account when determining their biological actions. Compound **147a** and ligand 3 (L3) showed more cytotoxic activity than cisplatin against the HCT 116 cell line, suggesting that they might be utilized for developing a novel class of thiosemicarbazone-based anticancer medicines. On the other hand, complex **147c**, which is more hydrophobic than complexes **147a** and **147b**, would make a good choice for research on antimalarial activity. Nevertheless, it was discovered that the substances that were cytotoxic did not also show strong antimalarial action [91].

Eight transition metal (II) complexes**148-155** of TSC derivative, with M:TSC ratios of 1:1 and 2:1, have been produced. Refat, Moamen S., et al. employed mass spectra, FTIR, UV-Vis, magnetic measurements, elemental analysis, molar conductivity, and thermogravimetric techniques to identify such complexes. For the Co(II) **148,152**, Ni(II) **149,153**, and Cu(II)**150,154** complexes, the electronic spectrum data supports an octahedral geometry, whereas Zn(II) **151,155** has four coordinated geometry. The presence of additional coordinated molecules (such as Cl, H_2O, or NH_3) in the composition of TSC complexes was demonstrated by the thermogravimetry analysis studies, and IR and micro analytical measurements verified this finding. When evaluated for antimicrobial action against a variety of pathogens, the ligand and its Co(II), Ni(II), Cu(II), and Zn(II) complexes **148-155** were shown to be more effective than Gentamycin and Gentumycin in vitro antibacterial activity. The findings of a molecular docking research against 4o1v kidney cancer and 3hb5-oxidoreductase breast cancer showed that the free TSC ligand was capable of attaching to 3hb5-oxidoreductase breast cancer [92].

The synthesis and Spectro analytical determination of nickel complex **156**with Schiff base vanillin-4-methyl-4-phenyl-3-thosemicarbazone, derived from natural aldehyde vanillin was carried out by Kumar, Lekshmi V., S. Sunitha, and G. Rathika Nath. For the nickel complex, an octahedral geometry was suggested based on the characterization methods. An analysis of antioxidants using the DPPH radical scavenging test reveals that the nickel complex**156** has a higher IC_{50} value of 46.35 ± 1.886 mg/mL than ascorbic acid, indicating significant radical scavenging action. The compound **156** has strong antidiabetic efficacy, according to the alpha amylase inhibitory test, with an IC_{50} value of 0.109 mg/mL, which is also greater than that of the common medication acarbose. The complex **156** may make an excellent medication for several diseases because it was shown to have strong cytotoxic action against the HeLa cervical cancer cell line and minimal cytotoxicity against normal cell line [93].

By reacting 4-(pyridin-2-yl)piperazine-1-carbothiohydrazide with 5-nitroisatin, Singh, Narendra Kumar, et al. were able to synthesize thethiosemicarbazone (Nitistpyrdlpz) ligand. The resulted ligand then refluxed with copper(II) chloride to produce copper(II) thiosemicarbazone (Cu-Nitistpyrdlpz)**157**. The ligand (Nitistpyrdlpz) and its Cu(II) complex **157** demonstrated anticancer activity against breast cancer cell lines; MCF-7 and MDA-MB-231 and epidermoid carcinoma. A431demonstrated that complex notably decreased the percentage of cell viability for all tested cell lines, but it was most effective against MDA-MB-231. At micromolar concentrations, it showed anticancer action against cell lines of both skin and breast cancer (IC_{50} 0.85-1.24 μM). By substituting on parent isatin and pyridyl piperazinyl rings and incorporating metal ions, ligands can become more potent against cancer. Due to its high binding affinity for DNA and excessive production of reactive oxygen species (ROS), copper atoms with physiologically accessible redox potentials are essential for the formation of N(4) modified copper(II) complexes, which have been shown to exhibit substantial anticancer activity. Therefore, the copper (II) complex (Cu-Nitistpyrdlpz) **157** against MDA-MB-231 (IC_{50} 0.85 μM) may be employed as a non-platinum anticancer drug[94].

By oxidizing divalent cobalt chloride in situ and adding it to the ligands, Fathy, Amany, et al. have synthesized novel complexes **158a-b**of trivalent cobalt with substituted thiosemicarbazone ligands HL^1 and HL^2 that contain an N,N,S donor system. The complexes were found to be 1:1 by conductometric investigations on their DMF solutions, and their diamagnetism demonstrated that the cobalt in the complexes **158a-b**was in a low-spin trivalent oxidation state. The compound was shown to crystallize in the triclinic space group P-1 by X-ray diffraction examination and exhibited in octahedral environment around the metal. The ligand HL^2 (20 mg/mL in DMSO) exhibited inhibitory zones measuring 10 mm against S. aureus and E. coli. The corresponding complex, at the same dosage, increased this activity to 15 and 12 mm against these strains of bacteria, respectively. The highest improved activity against the breast MCF-7 cells was found using the HL^1 screening assay on four human cancer cells. These findings hold greater significance when compared to analogous cobalt complexes, but they are not as effective when compared to

the 9.66 μM inhibition provided by doxorubicin. However, doxorubicin exhibited more cytotoxicity against BHK normal cells in comparison to the ligands, whereas the complexes showed much reduced toxicities towards normal BHK cells [95].

Density Functional Theory (DFT) Simulations and other Spectroscopic Characterizations:

The ligand 4-phenyl(2-methoxybenzoyl)-3-thiosemicarbazide (Hpmt) complexes with o-phen as a co-ligand were synthesized and characterized using TGA, magnetic susceptibility, single X-ray crystallography, and other spectroanalytical techniques. The complexes $Mn(pmt)_2$ (o-phen)] **159** and $[Zn(pmt)_2$(o-phen)] **160** displayed distorted octahedral geometry and crystallized in monoclinic systems with the space group P2/n. TGA study reveals that the complexes are stable up to 200 °C, suggesting the lack of coordinated and lattice water which ultimately resulted into the formation of $Mn(NCO)_2$ and $Zn(NCSNH)_2$ as the residue. The authors Singh, A., et al. also investigated HOMO-LUMO's of the prepared ligands and complexes. Low excitation energy for $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions is suggested by the Zn(II) complex's**160** relatively small HOMO–LUMO energy gap compared to the Mn(II) complex**159**. Weak intramolecular N-H···O, N-H···S, and C-H···S interactions maintain the crystal structures of both complexes, resulting in supramolecular design. Finally, the Density Functional Theory computation results validate the experimental data from X-ray investigations [96].

Bal-Demirci, Tülay, and co-authors synthesized nickel(II)**161a-b**, iron(III)**162a-b**, and oxovanadium(IV)**163a-b** complexes of 3-hydroxysalicylidene-S-methylthiosemicarbazone (L) via the combination of 3-hydroxysalicyldehyde-Smethylthiosemicarbazone with R1-substituted-salicylaldehyde (R1: H, 3-OH) and Ni(II), Fe(III), and VO(IV) as template ions. The ligand and its complexes were studied using spectroscopic techniques such as Uv/Vis., IR, ^{1}HNMR, EPR, and elemental analysis. By reducing copper(II) neocuproine (Cu(II)-Nc) using the CUPRAC technique, the in vitro antioxidant ability of the free ligand and its metal complexes were assessed. The iron(III) complex**162a-b** has a higher trolox equivalent antioxidant capacity (TEAC) value (3.27) than the other complexes. Thus, compared other complexes and ligand L the iron (III) complex **162b** showed more antioxidant capacity in the CUPRAC technique. Studies on the radical scavenging activity of reactive oxygen species (ROS), such as hydrogen peroxide (H_2O_2), hydroxyl radical (OH), and superoxide anion radical ($O2^{\bullet-}$), showed that the V(IV)**163a-b** and Fe(III) complexes**162a-b** in particular have large ROS scavenging activity [97].

According to Jayakumar, K., et al., copper(II) complexes**164a-h** of 2-benzoylpyridine-N4-methyl thiosemicarbazone (HL) were prepared in both mononuclear and binuclear forms and were studied using a range of spectroscopic techniques. The flexible nature of the thiosemicarbazone framework during complex formation is supported by the coordination mode of 2-benzoylpyridine-N4-methylthiosemicarbazone (HL) in both its neutral and thioiminolate form in the complexes. The structure of the sulfur bridged Cu(II) box dimeric complex**164h** with the iodine atom in the terminal position is an intriguing aspect of this work. The distinctive characteristics of this complex include the presence of ditholate bridges connecting non-symmetrically related [CuLI] units, the coexistence of basal and apical μ-thiolate bridges, and the production of persistent Cu(II)-I bonds. The complex $[Cu_2L_2I_2]$, a non-centrosymmetric box dimer, crystallizes in a monoclinic C2/c space group with a distorted square pyramidal geometry. All complexes show mono deprotonated thionic tautomeric coordination of the tridentate thiosemicarbazone, with the exception of the sulfato complex, $[Cu(HL)(SO_4)].H_2O$**164a**, where it binds to the metal atom in neutral form. Thermogravimetric analysis is used to determine the weight loss percentage of metal complexes. EPR is used to compute the spin Hamiltonian and bonding parameters [98].

Prabhu, Rupesh Narayana, and Samudranil Pal have described a simple approach for synthesizing cyclometallatedruthenium(II) carbonyl compounds**165a-f** using CNS-donor 1-pyrenaldehyde 4-R-3-thiosemicarbazones. Elemental (CHN) analysis, magnetic susceptibility, and various spectroscopic techniques including ESI-MS, IR, UV-Vis, emission, and 1H-NMR were used to characterize the complexes with the general chemical formula trans-$[Ru(L^n)(CO)(EPh_3)_2]$ (where E=P or As). The thiosemicarbazonate ligand ($(L^n)^{2-}$) exhibited a circularly spanning CNS coordination mechanism by the generation of 5,5-membered fused chelate rings, the azomethine-N, thioamidate-S, and 1-pyrenyl ortho-C atoms, as indicated by single crystal X-ray diffraction experiments. A distorted octahedral C_2NSE_2 coordination sphere around the ruthenium(II) center and regioselective activation of 1-pyrenyl ortho C–H form the CNS coordination mode of the thiosemicarbazonate ligand $(L^n)^{2-}$ is observed. Currently, employing synthetic procedures similar to those reported here, researchers are attempting to

isolate that were previously elusive pincer-type cyclometallated compounds with thiobenzhydrazones of polycyclic aromatic aldehydes [99].

The first known ionic gold(I) complex, $[Au(k^1\text{-}S\text{-}HL_3)_2]Cl$, was discovered by Lobana, Tarlok S., et al. when gold(I) chloride directly reacted with 3-nitrobenzaldehyde thiosemicarbazone in the presence of PPh_3. The study examines how substituents at the N^1/C^2 atoms of the thiosemicarbazones $R^1R^2C^2 = N^3\text{-}N^2H\text{-}C1(=S)\text{-}N^1HR^3$ affect the formation of gold(I) complexes. compounds **166a** and **166b** show that substituents (methyl and ethyl) at the N^1 atom play a crucial role in forming ionic compounds, eliminating the need for triphenyl phosphine. Complexes **166a**and **166b**are the first to result from direct reactions of gold(I) chloride with a thio-ligand, eliminating the need for PPh3 or an intermediary substrate. Complex **166a**, which has a methyl substituent at the N^1 atom, has two independent molecules in its crystal lattice, but complex **166b**, which has an N-ethyl substituent, has just one type of molecule in it. Both complexes exhibit strong fluorescence bands between 340-540 nm, which corresponds to an excitation wavelength of 308 nm. Because these complexes lack PPh_3 bonded molecules, synthesizing gold(I) ionic complexes may be beneficial from a biochemical perspective [100].

Two novel bis(thiosemicarbazone) ligands (H_2L1) and (H_3L2), along with their Copper(II)**167a-b** and Nickel(II) **168a-b**complexes, have been synthesized by Hosseini-Yazdi, SeyedAbolfazl, et al. and characterized by UV-Vis spectroscopy, FT-IR spectroscopy, elemental analysis, and single-crystal X-ray diffraction technique. When both ligands react with Ni(II) and Cu(II) acetates, they both lose their hydrazinic hydrogen atoms by coordination and become double negative anions. Two imine N and two S atoms coordinated with the metal centres in [NiL1] EtOH **168b**and [CuL1] MeOH**167b** complexes, exhibiting a distorted square planar coordination environment. These ligands function as the N_2S_2 donor set in all complexes; the hydroxyl group affects the electrochemical potentials and reversibility of MII/MI couples but has no effect on coordination geometry. In comparison to the nickel complex, the copper complex exhibits more geometric distortion from square planar. Cyclic voltammetry investigations of Cu(II) and Ni(II) complexes in DMF demonstrate their ability to stabilize low oxidation states of Cu(I) and Ni(I) [101].

The Mn complexes of various ligands including thiosemicarbazone ligands [Mn(ttfa)$_2$(bpy)] **169a** and [Mn(ipt)$_2$(o-phen)] **169b**were synthesized, and their spectral and crystal structure analyses were reported by Bharty, M. K., et al. They were obtained from a Mn(II) salt and the multidentate ligands Hpchcm and Hipt, which contain N, S, and O donor atoms. As revealed by the crystal structure of complex **169b**, comprising of carbonyl oxygen atoms and deprotonated hydrazinic nitrogen atoms, the ligand is attached to the Mn(II) core as ON uninegative bidentate fashion. The metal center of the complexes is surrounded by a distorted octahedral geometry. Different forms of intermolecular hydrogen bonding stabilize the complexes' crystal structures and generate supramolecular frameworks. The study of the thermal behavior of complexes in conjunction with the ligand Hpchcm has revealed that the complexes go through two or three stages of disintegration before producing MnO as the residue [102].

Using structural, analytical, and spectral approaches, GhodratMahmoudi et al. studied the synthesis of two novel pyridine-based heterocyclic thiosemicarbazone ligands and their Ni(II)**170a-b**, Cu(II)**171a-b**, Mn(II) **172**, Cd(II)**173**, and Cd(III)**174** complexes. surprisingly a novel ligand (L_3) is generated in the presence of Cu(II) as a result of an atypical cyclization**171a** of the thiosemicarbazone HL_2, which is facilitated by the metal center. There are seven complexes resulting from the coordination of two nitrogen and one sulfur donor atom in the mono-deprotonated anionic forms of the ligands. The metal centers of these complexes range from four-coordinated square planar to six-coordinated distorted octahedral. Using DFT simulations, it was examined the intriguing supramolecular assemblages of certain compounds that have been seen in the solid form. In the solid state with normal π–π distances, compounds 1-3 display intriguing antiparallel chelate−chelate and chelate–π stacking interactions that have been investigated using DFT calculations. The findings may be crucial to comprehending the solid-state architecture of systems of organic and inorganic materials containing metal-chelate rings and organic aromatic molecules [103].

Ni(II) complexes**175a-d** formed from dihydroxybenzaldehyde thiosemicarbazones (H_3L^1, H_3L^2, H_3L^3, H_3L^4) and 1,2-bis(diphenylphosphino)ethane (dppe) are synthesized and structurally characterized by Shawish, Hana B., et al. The observed results indicate that the thiosemicarbazone ligands exhibit tridentate ligand behavior, wherein they coordinate with the Ni(II) ion via the O, N, and S atoms. The collected experimental data imply that the thiosemicarbazone ligands exhibit tridentate ligand behavior, whereby the O, N, and S atoms coordinate with the Ni(II) ion, while the P atom coordinates the dppe ligand with the Ni(II) ion. Nickel is arranged in a square planar shape, as evidenced by absorption bands between 353 and 414 nm seen in the UV–Vis spectra of Ni(II) complexes [104].

Martínez, Javier, et al. have successfully synthesized thiosemicarbazone tetranuclear palladacycles in high yields by employing potassium tetrachloropalladate(II) in ethanol, lithium tetrachloropalladate(II) in methanol, or palladium(II) acetate in glacial acetic acid. The organic moiety attaches to palladium in a tridentate [C,N,S] pincer manner in every instance. Only one Pd-S bond is broken down in response to diphosphines, allowing for the synthesis of mononuclear species**176a-b** that can act as metalloligands or dinuclear complexes, which are the building blocks of novel bimetallic compounds. X-ray diffraction analysis was used to identify the molecular structure of complex **176k**, as well as of both the ligands. With a slightly distorted square-planar coordination

geometry, the palladium atoms in complex **176k**.$CHCl_3$ are bonded to four distinct donors: a phosphorus atom of trans bis(diphenylphosphino) ethene and a tridentate thiosemicarbazone through the aryl carbon, the imine nitrogen, and the thioamide sulfur atom. In order to determine the structural components of the species for which there were no X-ray data, Density Functional Theory (DFT) simulations have also been used to characterize the ligands and complexes. The rotation of the thiosemicarbazone group around the phosphine bridge and the P-Pd bond is analyzed in the present work [105].

Anthony B. Carter and colleagues have demonstrated the synthesis and characterization of a family of 1,8-naphthalimide containing sulfonate anions and their subsequent incorporation into thiosemicarbazone-based Fe(III) complexes**177a-e**. Extended structures with layered topologies, where anions engage with cations by H-bonding and, most of the time, π-stacking interactions, are shown in three of the four structurally described complexes containing the naphthalimide anions. Furthermore, the orderly immobilization of functional transfers onto a quartz slide may be made possible by the layer development, demonstrating the capacity of designer anions to give functionality to complexes. The techniques shown here are perfect for developing supramolecular materials since they are synthetically straightforward and do not necessitate the time-consuming synthetic approaches that are typically needed to incorporate structure-directing groups into ligand scaffolds. A library of functional anions that can be added to a wide variety of metal complexes is also made possible by this method, which may lead to the formation of multifunctional systems in which the anion is essential to the ordering and structure of the system. This method of introducing structure-directing agents into coordination complexes is relatively simple, and it may lead to the synthesis of a wide variety of new metallosupramolecular materials in which functional metal complexes can be deposited onto surfaces or organized into layered materials for possible applications [106].

Using the reaction of the corresponding chalcone with 4-phenyl-3-thiosemicarbazide and HCl in EtOH, Barbosa, Igor Resendes, et al. prepared and characterized four chalcone–thiosemicarbazones (C-TSCs) of type 2-((E)-3-(4-R-phenyl)-1-phenylallylidene)-N-phenylhydrazinecarbothioamide ligands as well as their Cu(II)**178a-d** and Zn(II)**179a-d** complexes. The proligands are known to exist in two tautomeric forms in solution, designated as E and Z isomers, according to spectroscopic investigations. The Z form becomes preferable for the complexes upon coordination. X-ray diffraction was used to identify the crystalline structures of two Zn(II) complexes **179b, 179d** and two Cu(II) complexes**178a, 178c**. The ligand HL4 was the most detrimental derivative, displaying cell viability at roughly 50%, when the actions of compound were evaluated on yeast. However, out of all the compounds examined, HL1 was found to best trigger lipid peroxidation. The toxicity of the ligand towards S. cerevisiae was not increased by coordination with Cu(II) or Zn(II). Furthermore, despite the Cu(II) complex showing a twofold increase over Zn(II), complexes **178a** and **178b** did not cause significant amounts of membrane damage [107].

Zinc(II) has reacted with 5-nitro-salicylaldehyde-N1-substituted thiosemicarbazones and 4, 4'-dimethyl-2, 2'-bipyridine (dm-bipy), 2, 9-dimethyl-1, 10-phenanthroline (dm-phen), and 3, 4, 7, 8-tetramethyl-1, 10-phenanthroline (tm-phen) as co-ligands to produce complexes of [Zn(Ln)(L)]**180a-l**. These compounds have been examined as co-ligands in single crystal X-ray crystallography, elemental analysis, and infrared and electronic absorption spectroscopy. Complexes**180i** and**180j** exhibit distorted trigonal bipyramidal geometry, whereas complexes **180e**, **180h**, and **180k**exhibit distorted square pyramidal geometry. The complexes exhibited strong bands of fluorescence at ε_{max} = 434-440 nm. It was observed that the fluorescence of dmphen and tm-phen was higher than that of dm-bipy co-ligands. The bio-activity of complexes **180a-l** including dm-bipy, dm-phen, and tm-phen as co-ligands is higher at low mic values in relation to Methicillin-resistant Staphylococcus aureus (MRSA) than that of comparable Zn(II) complexes with bipy and phen. Compounds have been discovered to have more bioactivity against Klebsiella pneumonia 1 and Candida albicans than comparable Zn(II) complexes that have been documented in the literature. Lastly, the present compounds are less potent and require high mic concentrations against Salmonella typhimurium

1. Only a small number of complexes demonstrated activity against E. coli, while complexes displayed excellent activity against Enterococcus faecalis without any comparable studies in the literature to compare with [108].

El-Saied, Fathy A., et al. synthesized quinoline-2-caboxyaldehyde thiosemicarbazone (HL_1) and quinoline-2-caboxyaldehyde N-dimethyl thiosemicarbazone (HL_2) metal complexes, which were then studied by means of analytical and spectroscopic methods. According to the results, the ligands formed square planar, octahedral, or tetragonal distorted shapes around the central metal ions via bonding through the N of the azomethine, the N of the quinoline ring, and the S atoms in thiol or thion form. The findings of the anti-neurotoxic action of ligands and their complexes indicate that aluminum exposure increases oxidative stress in the brain, however concurrent thiosemicarbazone complexes may potentially mitigate this effect. Aluminum's effects may be due to a direct toxic effect, which is linked to an increase in ROS but causes a decrease in protein synthesis. Complexes **181-187**may be influencing the absorption or excretion of aluminum because of their chelating activity, which alters the amount of aluminum that is exposed to internal organs. These findings may clarify the clinical significance of thiosemicarbazone complexes in Alzheimer's disease [109].

Başaran, Eyüp, et al. characterized the two new chiral thiosemicarbazide ligands and their Cu (II)**188a-b**, Ni (II)**189a-b**, Pd (II)**190a-b**, and Zn (II) **191a-b** complexes, various analytical techniques were used, including mass, elemental analysis, Fourier transform infrared (FT-IR), ultraviolet visible (UV-Vis), and NMR exclusively for the ligand. Upon examination of the magnetic susceptibility measurements, it was observed that the complexes had a

square planar structure, with the compounds belonging to groups (a) and (b) acting as ligands and their respective complexes being enantiomers of one another. When newly synthesized compounds were compared to standards, their antioxidant activity revealed a mild scavenging of DPPH activity. The order of antioxidant activity of the complexes for the given metals is as Pd > Ni > Cu > Zn. It was shown that the structure-activity connection of complex products that the antioxidant activities of a group of compounds, known as the (R) enantiomer, were superior to those of the group b substances, known as the (S) enantiomer. Furthermore, compared to Ni (II), Cu (II), and Zn (II) complexes, Pd (II) **190a-b**complexes showed superior antioxidant activity. As a result, both Pd complexes **190a-b** can be employed as test standards or antioxidant agents [110].

In 1M hydrochloric acid (HCl) media, Hazani, N. N., et al. investigated the potential of the Schiff-base ligand combination 2-acetylpyridine 4-ethyl-3-thiosemicarbazone (LH) and its organotin(IV) complex ($BuSn(L)Cl_2$) **192**as a corrosion inhibitor for mild steel. A diffraction investigation using X-ray crystallography, elemental analysis, FT-IR, UV-Vis, and NMR spectroscopy were used to confirm the chemical structures of the synthesized compounds. Based on its pyridyl, azomethine nitrogen, and thiolate sulfur, the structure demonstrated that the LH acted as a tridentate (N, N', S) donor to tin. Using the conventional weight loss method, the corrosion inhibition properties of the free Schiff-base ligand and its organotin complex were investigated. Both inhibitors complied with Langmuir's adsorption isotherm, however $BuSn(L)Cl_2$**192** demonstrated a higher inhibition efficiency than LH. A study on the adsorption isotherm and weight loss of mild steel in 1M HCl revealed that LH and $BuSn(L)Cl_2$ have the potential to be employed as corrosion inhibitors [111].

Handy, Omar Abdullahi Wafudu, Mohamad Shazwan Shah Jamil, and Mustaffa Shamsuddin synthesized a novel copper(I) complex**193** of 2-acetylpyridine-N(4)-(methyl phenyl)thiosemicarbazone-tris-(triphenylphosphine) nitrate and characterized using a variety of spectroscopic techniques, like UV, IR, ^{1}H and $^{13}CNMR$, thermal gravimetric analysis (TGA), CHN elemental analyses and molar conductivity analysis. The complex **193** was thermally decomposed to produce copper oxide, demonstrating that copper oxide had more catalytic activity than the complex itself. The copper oxide catalyst was optimized by altering its quantity (0.5, 1.0, 1.5, and 2.0 mol%), resulting in conversion rates of 96.7, 98.7, 95.4, and 89.6%. Based on the findings, the ideal catalyst loading for the conversion of 4-nitrophenol to 4-aminophenol was 1.0 mg. Copper oxide recyclability and reproducibility experiments show that this catalyst is extremely efficient, has great reproducibility, and can be reused four times without significantly decreasing catalytic activity [112].

Jawaria, Rifat, et al. characterized and assessed the inhibitory potential of the transition metal complexes (Cu(II)**194a-k** and Co(II)) of ferrocene-based thiosemicarbazones that had previously been synthesized by condensation of various thiosemicarbazides with acetylferrocene in the presence of a catalytic amount of acetic acid. In general, the ligands and their metal complexes exhibited moderate to strong inhibitory action against the specified enzymes. It was discovered that every Cu(II) complex **194a-k**exhibited greater potency when compared to either their ligand or other metal complexes. Comparably, the Co(II) complexes under investigation also demonstrated strong inhibition of enzymes, with IC_{50} values that were somewhat higher than those of Cu(II) complexes but still much greater than the conventional "Eserine." The structure-activity connection of the compounds was validated by in silico investigations [113].

Matesanz, Ana I., et al. synthesized and characterized Pd (II) complexes **196a-c**of three thiosemicarbazone derivatives: 4-(dimethylamino)-benzaldehyde 4,4-dimethylthiosemicarbazone (HL_1), 4-(dimethylamino)-benzaldehyde thiosemicarbazone (HL_2), and 4-(dimethylamino) benzaldehyde 4-methylthiosemicarbazone. The crystal structures of $Pd(L_2)_2$**196b**and $Pd(L_3)_2$**196c**, two coordination compounds, revealed the anticipated square-planar environment for the metal centers. Palladium-(II) complexes and TSCN ligands, in order to assess which one is more effective at preventing Aβ aggregation. The collected data demonstrate that TSCN-based compounds are effective anti-aggregation agents, and as such, they should be taken into account in future studies aiming at creating anti-AD medications. The palladium(II) complexes were also found to be significantly more effective inhibitors than the free TSCN ligands in cellulo experiments with E. coli expressing Aβ(1–42), demonstrating the beneficial effect of metal coordination and promoting the widespread use of bacterial inclusion bodies as an extra experiment to support in vitro studies [114].

The synthesis crystal structures, and spectroscopic characterisation of later first-row transition metal complexes with hydroxyacetone-derived N4-methyl substituted thiosemicarbazone was described by Kotian, Avinash, and colleagues. The Co(II) **197** and Ni(II) **198** complexes adopts in monoclinic and triclinic crystal systems, respectively, according to the crystal structures. The central metal ions are connected to the ligand, 1-(1-hydroxypropan-2-ylidene)-N4-methylthiosemicarbazone, in a neutral, S,N,O tridentate manner. Over the centers of the Co(II), Ni(II), and Zn(II) metals, the ligand environment creates a distorted octahedral geometry while around the Cu(II) ion, it forms a square pyramidal geometry**200**. The synthesized compounds are four times more active than the standard medicine Streptomycin and two times more active than the other two standards employed, Pyrazinamide and Ciprofloxacin, according to the in vitro antitubercular findings against Mycobacterium TB [115].

The Ni (II) complex**201** of ligand (LH) 4-(diphenylamino)benzaldehyde-4-(2-fluorophenyl)thiosemicarbazone were synthesized and characterized by Osman, Uwaisulqarni M., et al. using spectrometric techniques, X-ray studies, magnetic susceptibility, and molar conductivity. The LH ligand exhibits mononegative bidentate behavior through azomethine (N=C) and (C-S) groups with Ni(II) metal ion, revealed by the FTIR spectra. Electronic spectra, Magnetic measurements and Single X-ray crystallography was used to validate the square planar geometry of Ni(II) complex**201**. Polymer electrolyte (PE) films were fabricated by solution casting and conductivity tests were performed. Using Electrochemical Impedance Spectroscopy (EIS), the conductivity of the produced PE films was investigated [116].

By using 4-methoxysalicylaldehyde-N-phenylthiosemicarbazone and 3,5-lutidine, Altiparmak, ElifAvcu, et al. obtained mixed ligand complexes of copper (II) **202**and nickel (II)**203**. Elements analysis, IR, UV, ^{1}H NMR, and ESI-MS spectra, in addition to magnetic susceptibility studies, have all been used to describe the structures of the complexes. Using the single-crystal X-ray diffraction method, it was discovered that complex **202** had a distorted square planar geometry and that the atoms of pyridyl nitrogen, thiolate sulfur, azomethine nitrogen, and phenolate oxygen were coordinated. The DFT/HSEH1PBE approach has also been used for quantum chemical DFT computations, employing the LANL2DZ basis set for the metal atom and the cc-pVDZ basis set for the C, H, N, O, and S atoms. The trolox equivalent antioxidant capacities (TEAC) of the ligand and its metal complexes were determined by using CUPRAC and DPPH tests to examine their antioxidant properties. According to CUPRAC, the total antioxidant capacity (TEAC) values decline in the order complex **203**> complex **202**> ligand; in terms of free radical scavenging (FRS), the order is ligand > complex **203**> complex **202**. We may conclude from a comparison of the complexes that complex **203** exhibits the highest antioxidant performance and radical scavenging, with values for complex **203** being larger than those of complex **202**. This is based on the assumption that "low oxidation potential" indicates "strong antioxidant power" [117].

Thuy, Pham Thu, et al. prepared the novel ligand N-methylanthraniloyl(4-ethylthiosemicarbazide) H_2L by treating anthranilic acid hydrazide and ethyl isothiocyanate in 100% ethanol. The various spectroscopic methods were used for characterization and analysis of the compounds. Ligand H_2L and o-phenanthroline reacted with $[Cu(MeCN)_4](PF_6)$ in methanol to form a cationic Cu(II) trinuclear complex**204**, which was separable into PF_6^- salt, which is composed of $[Cu_3(L)_2(o\text{-}phen)_2](PF_6)_2$**204**. The analysis of X-ray crystallographic and spectroscopic data revealed that H^2L deprotonates the protons in hydrazide, and the resultant dianion $\{L^{2-}\}$ functions as a bridging ligand, with most possible donor atoms forming stable chelates with Cu(II) ions. Specifically, a deformed square planar coordination mode with trans configuration is adopted by the central Cu(II) ion through its coordination with two dianions $\{L^{2-}\}$ via (O, N^2) donor sets. The coordination spheres of the two terminal Cu(II) ions are made up of (S, N^1, N_{amine}) and (N,N) donor sets that belong to $\{L^{2-}\}$ and ophenanthroline, respectively. The studies on magnetic properties and potential catalytic activities are going on [118].

In a one-pot reaction involving 2,3-dichloro-1,4-naphthoquinone, thiosemicarbazides, Ph_3P, and triethyl amine (Et_3N) as a catalyst, Alshammari, Mohammed B., et al. obtained new 1,4-naphthoquinone derived by triphenylphosphaneylidene (Ph_3P) and N-substituted-hydrazine-1-carbothioamides. Spectroscopic and X-ray structural studies were used to determine the ligand structures. The reaction was Eschenmoser nucleophilic addition. The study examined the complexation of freshly synthesized ligands with $CuCl_2$ and Ph_3P. Quantum mechanical simulations with the DFT approach proved the stability of the synthesized complexes**205a-f** [119].

By using HL (picolinoyl(4-ethylthiosemicarbazide), o-phenanthroline, $CuCl_2$, and base pyridine, Nguyen, Hung Huy, et al. synthesized a novel heteroleptic cationic Cu(II) complex**206** with the composition of $[Cu(L)(o\text{-}phen)]^+$. The obtained Cu(II) complex **206** has been studied using X-ray crystallography and spectroscopy techniques. The findings show that the compound $[Cu(L)(o\text{-}phen)](PF_6)$ is a heterocyclic complex, where the Cu(II) ion is five coordinate with (N, N)-bidentate o-phenanthroline and singly deprotonated (S, N^1, $N_{pyridine}$)-tridentate ligand $\{L^-\}$ [120].

3-Benzylidene-2,4-pentanedione-S-methyl-thiosemicarbazone hydrogen iodide (TSC), a novel thiosemicarbazone derivative was synthesized by Karakurt, Tuncay, et al. and characterized with the help of elemental analysis, IR, ^{1}H NMR, and single crystal X-ray diffraction. Ni (1-4), a new nickel(II) complexes**207a-d**, were synthesized from TSC and salicylaldehyde using the template effect of nickel(II) ions. Spectroscopic evidence suggested that the alcohols were added by Michael to the 2,4-pentanedione moiety of the TSC, resulting in the formation of the complexes. Through single crystal X-ray diffraction, the distorted square planar structures of the complexes Ni**207a** and Ni**207b**were verified. Moreover, the theory DFT for the empirically acquired TSC, Ni1, and Ni2 structures was used to carry out the comprehensive calculations. The FMO levels produced by DFT calculations demonstrate that the antioxidant potential is constrained by chemical hardness, which is in line with the observed TEAC values. The TSC exhibited more activity than the self-derived nickel(II) complexes when the antioxidant capabilities of the compound were assessed using the DPPH and CUPRAC tests [121].

Conclusion:-

Thiosemicarbazones and their metal complexes are recognized for their broad spectrum of pharmaceutical properties, encompassing antibacterial, antimalarial, antiviral, antifungal, antiparasitic, and antitumor activities. These compounds, derived from the reaction of thiosemicarbazide with carbonyl-containing compounds, exhibit a diverse range of biological activities, making them significant in medicinal chemistry and drug development. The incorporation of metals into thiosemicarbazone structures often enhances their biological activity, stability, and selectivity. Metal complexes of thiosemicarbazones can exhibit synergistic effects, providing an additional dimension to their pharmacological profiles and expanding their potential therapeutic applications. The biological activity of thiosemicarbazones and their metal complexes is significantly influenced by both the structure of the parent aldehyde or ketone and the presence of bulky groups at the terminal nitrogen of the thiosemicarbazone moiety. The incorporation of bulky substituents at the terminal nitrogen of the thiosemicarbazone structure plays a crucial role in modulating its biological activity. Such bulky groups can introduce steric hindrance, which affects the spatial arrangement of the thiosemicarbazone molecule and enhances its ability to interact with specific biological targets. This steric effect often leads to an increase in biological activity, as the modified structure may better fit or interact with target sites, thus improving efficacy. The maximum biological activity of thiosemicarbazones and their metal complexes is observed when the N(4) position is disubstituted or integrated into a ring system. These structural features contribute to improved interaction with biological targets by altering the steric and electronic properties of the molecule, enhancing its stability, and optimizing its overall efficacy. It is important to highlight that metallated compounds have demonstrated significantly more promising pharmacological activities compared to conventional thiosemicarbazones. This enhanced efficacy underscores the potential of these compounds and strongly suggests the need for further research to explore and validate their therapeutic applications.

In this review, we emphasize the study of metal complexes derived from N(4)-substituted thiosemicarbazones, examining their diverse biological properties and their structural characterization through various spectrochemical

methods. The DNA binding and cleavage properties of various N(4)-substituted thiosemicarbazone metal complexes were investigated using techniques including viscometric measurements, gel electrophoresis, fluorescence spectroscopy, and heat denaturation assays. The results indicated that the complexes bind to DNA via intercalation, and substituting the phenyl ring in the thiosemicarbazone ligand increases cytotoxicity by enhancing the activity of complexes. Based on the results of the DNA binding investigations, it can be inferred that the complexes exhibit a significant tendency to bind to DNA, with interactions occurring predominantly through electrostatic forces. The findings are important for advancing the design of late first-row transition metal complexes and for evaluating their DNA binding and cleavage activities for potential therapeutic applications.

The cytotoxic properties of N(4)-thiosemicarbazone metal complexes were investigated against various carcinogenic cell lines, with the IC50 values being studied to evaluate their efficacy. It has been demonstrated that metal complexes with bulkier ligands, such as N(4)-methyl(phenyl)thiosemicarbazone, exhibit significant cytotoxic and antitumor effects in vitro, suggesting their potential application as anticancer agents. The antibacterial and antifungal activities of N4-substituted thiosemicarbazones and their metal complexes have been extensively investigated. The complexes were evaluated for their antibacterial and antifungal activity against a range of pathogenic bacterial and fungal strains. The study suggest that incorporation of bipy and phen co-ligands, which have a higher affinity for penetrating cell membranes, may enhance the lipophilicity of these complexes and subsequently improve their antimicrobial activity. It was found that the activity of the complexes achieves effectiveness comparable to the conventional bactericide streptomycin, in contrast to the simple ligand.

The additional applications for these complexes include the treatment of cancer and other life-threatening diseases. The complexes exhibit significant therapeutic potential against a wide range of human cancer cells, including COLO-205 and K-562, A2780 ovarian cancer cells, as well as pancreatic (BxPC3 and PSN1), colon (HCT-15), and MCF-7 breast cancer cells. Notably, these complexes may be evaluated as a novel therapeutic strategy to overcome multidrug resistance in cancer therapy. Lastly, scientists examined the intriguing chemical interactions and structures, such as chelate-chelate and chelate-π stacking, present in the solid forms of several compounds using Density Functional Theory (DFT) simulations. The N(4) substituted thiosemicarbazone metal complexes preparation techniques presented in this review are easy to comprehend and maybe a key draw for the future development of adaptable molecules with a wide range of uses.

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