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Publisher

Multidisciplinary Digital Publishing Institute (MDPI)

SJR 2025

0.254

Q3

H-Index

25

Publication type

Journals

ISSN

26734591

Coverage

2020-2025

Information

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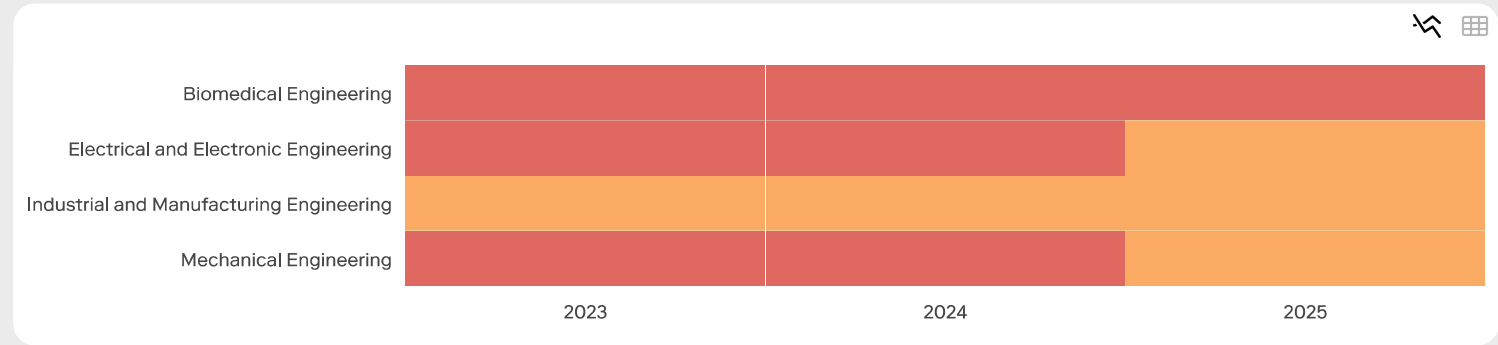
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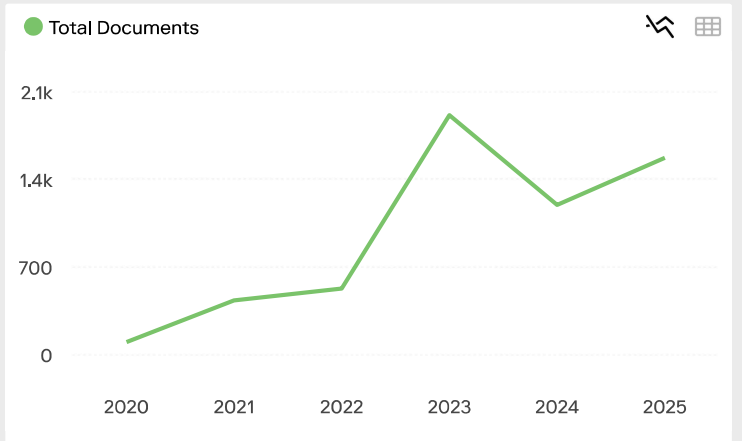
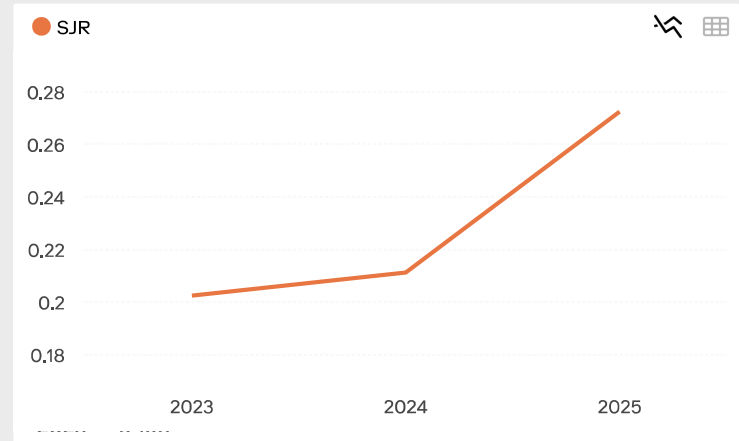
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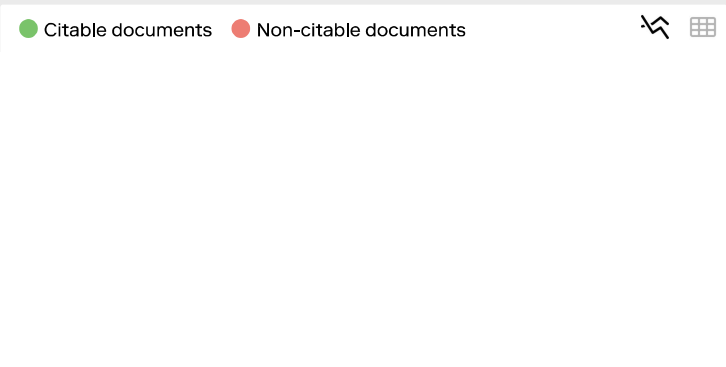
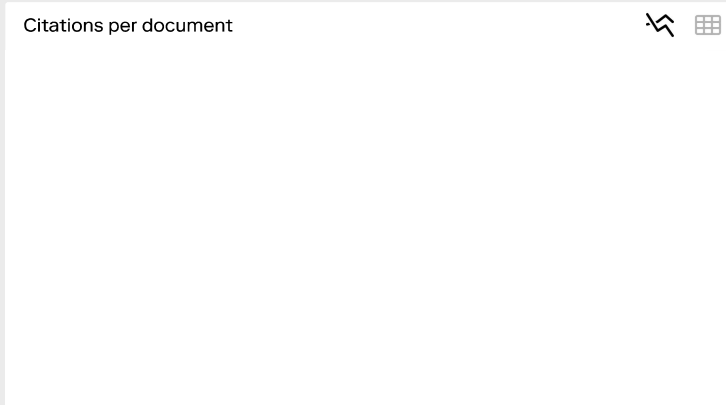
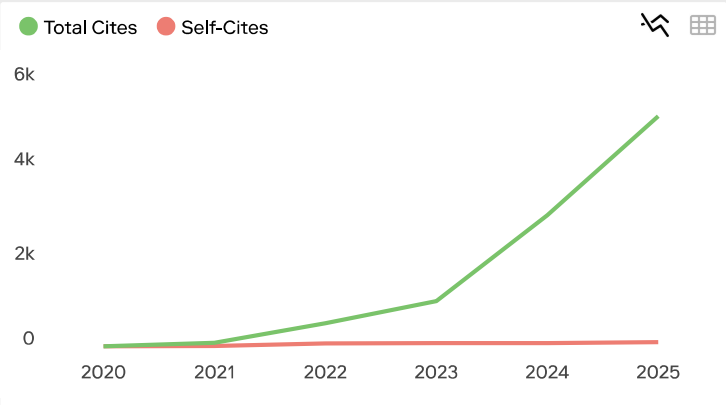
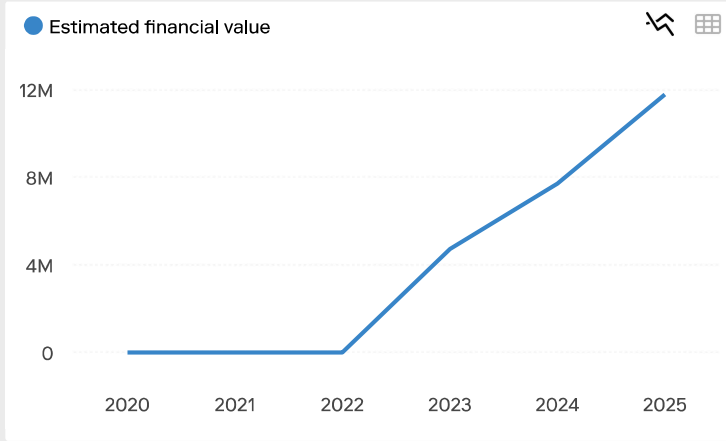
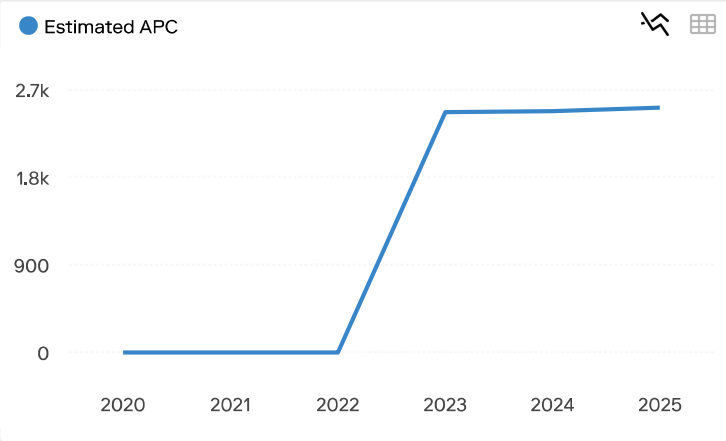
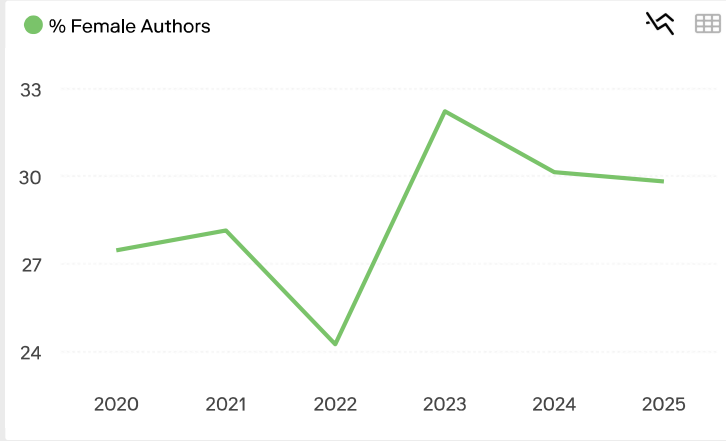
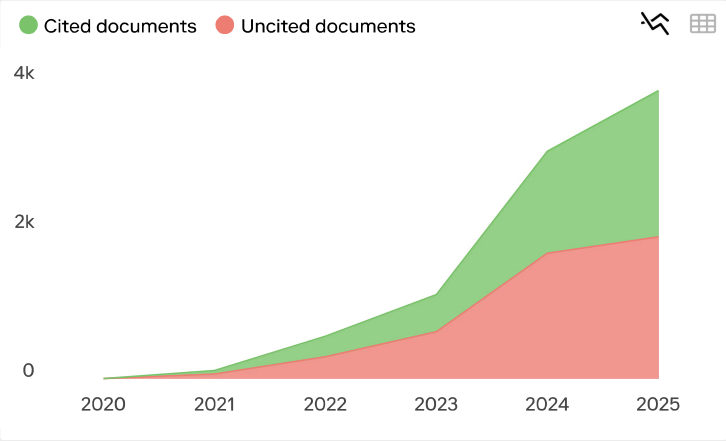
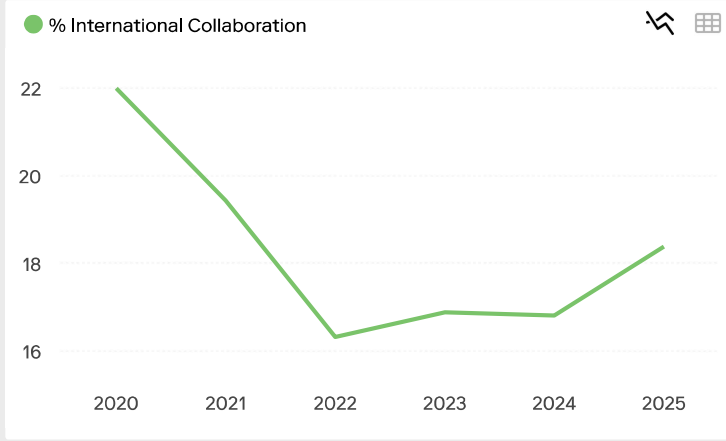
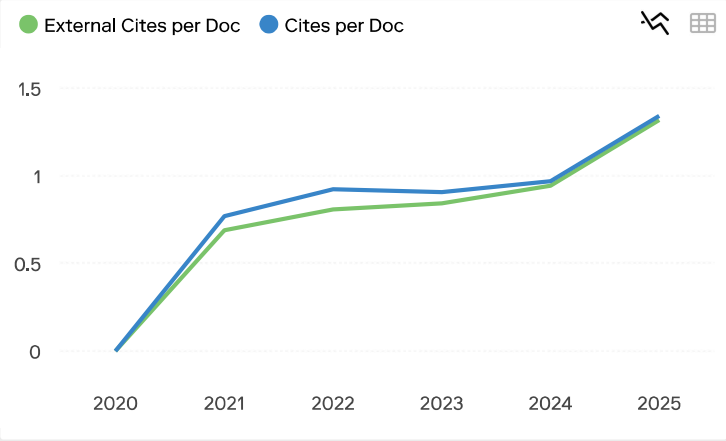
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Computational Studies of Thiosemicarbazone-Based Metal Complexes and Their Biological Applications [†]

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[†] Presented at the 4th International Electronic Conference on Processes, 20–22 October 2025; Available online: <https://sciforum.net/event/ECP2025>.

Abstract

Thiosemicarbazones are known for their versatile coordination behavior and wide-ranging applications in the field of materials science, catalysis, and medicinal chemistry. Several investigations have reported on the biological potential of transition metal complexes of TSCs. In addition, the structural, electronic, and reactive properties of these complexes are explored through computational studies using molecular docking and density functional theory (DFT). Such investigations not only support the interpretation of experimental results but also influence synthetic design by predicting the structural behavior of the complexes. In this study, we explore the computational studies of thiosemicarbazone metal complexes along with their biological activities.

Keywords: thiosemicarbazones; metal complexes; density functional theory; molecular docking; biological activity



Academic Editor: Blaž Likozar

Published: 13 January 2026

Citation: Hashmi, K.; Satya, P.; Veg, E.; Khan, T.; Joshi, S. Computational Studies of Thiosemicarbazone-Based Metal Complexes and Their Biological Applications. *Eng. Proc.* **2025**, *117*, 23. <https://doi.org/10.3390/engproc2025117023>

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1. Introduction

Thiosemicarbazones (TSCs) are organic compounds that have attracted significant research interest due to their diverse chemical properties and wide-ranging applications in various scientific domains [1]. The basic structure of TSCs consists of a central C-atom that is bonded to S, N and two H-atoms. TSCs are an important compound that are formed by the condensation reaction of thiosemicarbazides with appropriate aldehydes or ketones (Figure 1) [2].

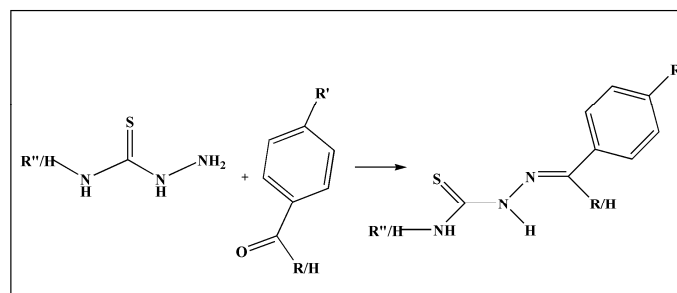


Figure 1. General method of preparation of TSCs.

This unique arrangement offers many molecular modification opportunities [3]. Various compounds, including bioactive molecules and metal complexes, have been synthesized by researchers using the unique reactivity of TSCs. These complexes display a wide range of biological activities, making them valuable scaffolds for developing novel therapeutic candidates. Due to their distinct chemical properties, transition metal complexes of different ligands are essential for a variety of biological activities. Zn, Cu, Ni, and Co TSC complexes have been extensively studied due to their significant structural, electronic and biological applications [4]. Because of their numerous desirable abilities, including coordination ability, stability, lipophilicity, chelation, diverse structural motifs, reactivity, DNA binding ability, etc., these complexes are very useful in catalysis, materials science and medicinal chemistry. Thus, these complexes are used in medicinal chemistry for the development of drugs and a variety of treatments. These compounds possess diverse functionalities that are crucial in various biological processes and applications, including antibacterial, antioxidant, anti-inflammatory, antimalarial, antifungal and anticancer properties [5,6]. The application of computational methods in chemistry and biology is crucial for drug discovery, providing valuable predictions across various research fields and industries, which are often challenging or time-consuming to achieve through experimental methods alone [7]. In the field of medicinal development, molecular docking, ADMET and DFT studies are essential tools [8,9]. They are used to predict the stability, chemical reactivity, toxicological and pharmacokinetic properties of the molecules, as well as to investigate the coordination between biological targets and possible drug molecules [10].

2. TSCs and Their Metal Complexes

Bal-Demirci et al. reported 3-hydroxysalicylaldehyde-S-methylthiosemicarbazone and their VO(IV), Fe(III), Ni(II) complexes (Figure 2). The parent ligand and its complexes have been evaluated for their antioxidant and Reactive Oxygen Species (ROS) radical scavenging activities. The Fe(III) complex showed superior antioxidant activity, while the complexes of Fe(III) and V(IV) demonstrated higher ROS scavenging properties than the free ligand [11].

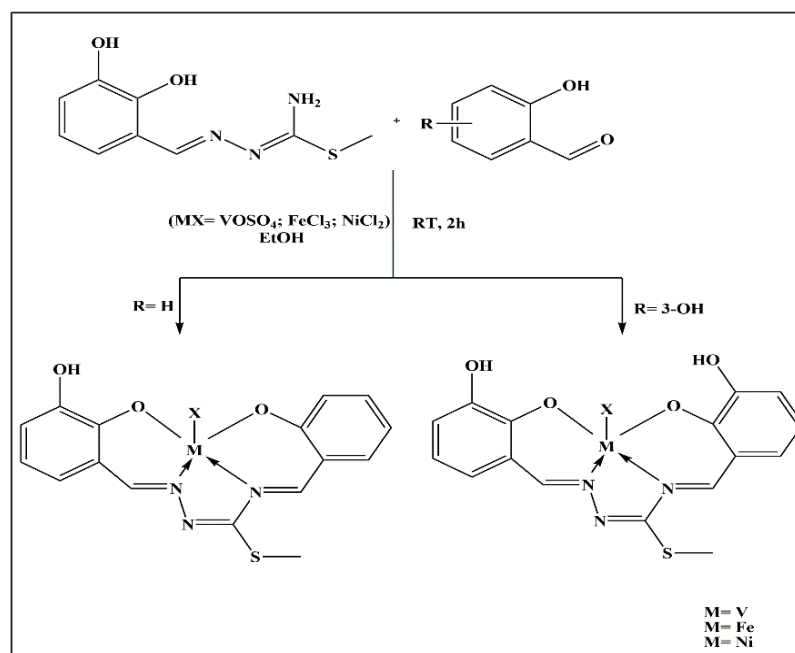


Figure 2. Metal complexes of 3-hydroxysalicylaldehyde-S-methylthiosemicarbazone.

Mitesh et al. also reported a series of Co(II), Ni(II), Cu(II), Zn(II) complexes with 3-chlorovanillin thiosemicarbazone (3-CVTSC) ligand (Figure 3). The antimicrobial activity

of 3-CVTSC and its metal complexes was also assessed. The complexes of Ni(II) and Zn(II) were found to be more effective than the ligand against the tested bacteria, and the Zn(II) and Co(II) complexes showed higher potency against the fungal strains [12].

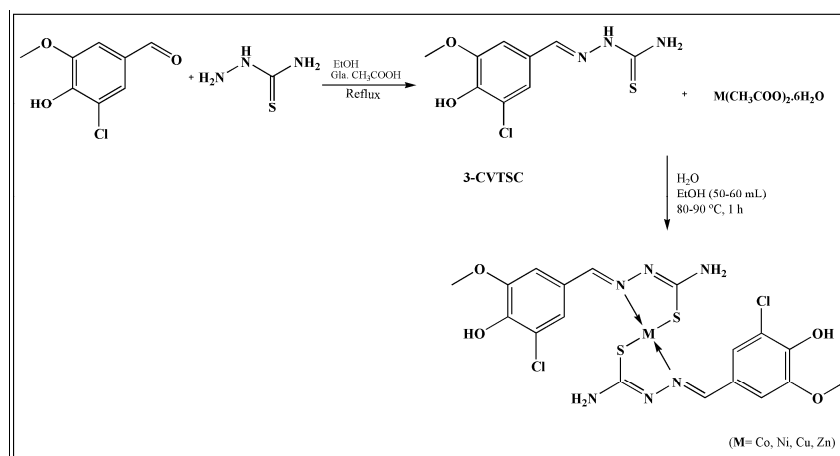


Figure 3. Metal complexes of 3-chlorovanillin thiosemicarbazone.

Similarly, Ahmed et al. synthesized 2,6-pyridinedicarboxaldehydethiosemicarbazone (PDCTC) ligand and their Cr(III), Co(II), Ni(II) and Cu(II) complexes (Figure 4). The antibacterial activity of the free ligand and its complexes against *S. aureus* and *E. coli*, along with two fungi, viz. *Candida albicans* and *Aspergillus niger* were also investigated. The complexes have greater bactericidal activity than the free ligand due to chelation [13].

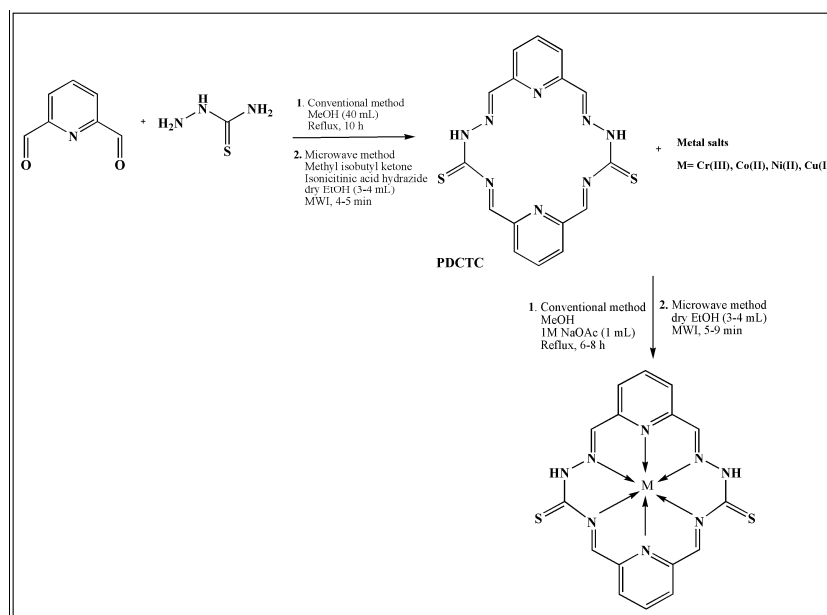


Figure 4. Metal complexes of 2,6-pyridinedicarboxaldehydethiosemicarbazone.

In another study, Rai et al. also reported 2-butyl thioquinazoline-4-(3H)-thiosemicarbazone (BTQT) ligand and their Co(II), Ni(II), and Cu(II) complexes (Figure 5). The antimicrobial activity of the ligand and complexes was tested against *C. albicans* and *E. coli*. Antimicrobial activity showed that the metal complexes have higher activity than the free ligand [14]. Some TSC metal complexes and their biological applications are depicted in Table 1.

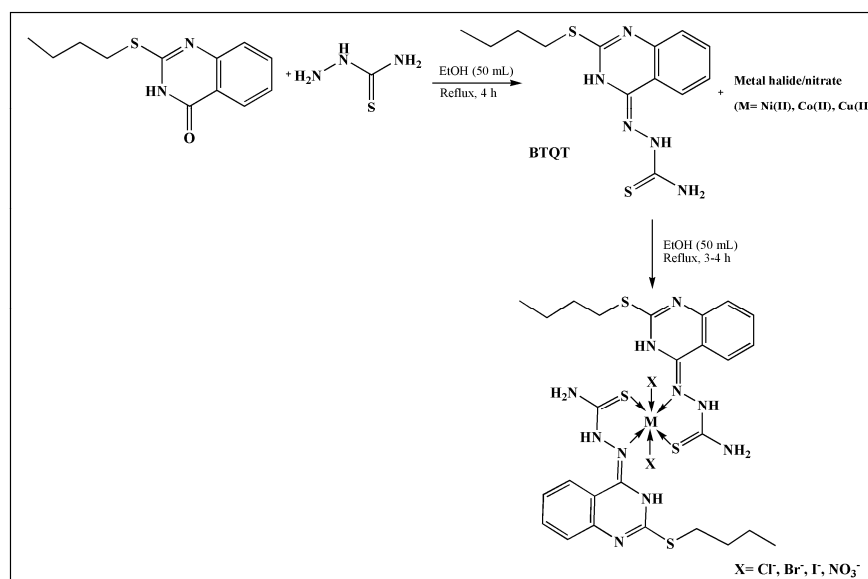


Figure 5. Metal complexes of 2-butyl thioquinazoline-4-(3H)-thiosemicarbazone.

Table 1. Biological application of some TSC metal complexes.

S.No.	Metal	TSC Ligand	Biological Activity	References
1.	Cu(II), Co(II), Ni(II) and Zn(II)	ethyl (E)-2-cyano-3-(2-((E)-3-ethyl-2-hydroxybenzylidene)hydrazine-1-carbothioamido)-3-(4-ethylphenyl)acrylate	Antifungal, Antibacterial	[15]
2.	Cu(II)	α -Heterocyclic-N4 -Substituted TSCs	Antiproliferative	[16]
3.	Pd(II), Pt(II)	3,5-diacetyl-1,2,4- triazol mono(4-phenylthiosemicarbazone)	Antiproliferative	[17]
4.	Ru(II)	(E)-2-(1-(5-substituted thiophen-2-yl)ethylidene)-N-substituted hydrazine-1-carbothioamide	Anticancer	[18]
5.	Cd(II)	4-benzyloxy-benzaldehyde-4-methyl-3-thiosemicarbazone	Anticancer	[19]

3. Computational Studies

The biological activity of the methoxy thiosemicarbazone (MTSC) ligand was validated in a previous study by performing an *in silico* molecular docking analysis using Docking Server, in which its binding interactions with the 3hb5-oxidoreductase breast cancer protein and the SPOP kidney cancer protein were investigated (Figure 6A,B) [20]. The MTSC free ligand has a negative binding score of $-5.83 \text{ kcal mol}^{-1}$ against 3hb5-oxidoreductase protein, suggesting that the interaction was thermodynamically favorable. The binding affinity of the MTSC ligand for the 3hb5-oxidoreductase active sites increases as affinity energy decreases, resulting in stronger inhibition. The hydrogen-bonding interactions formed between the MTSC ligand and the amino acid residues of the 3hb5-oxidoreductase protein were examined to determine the stability of the ligand. The MTSC ligand binds effectively to the cavity of the 3hb5-oxidoreductase protein, facilitated by multiple hydrogen bonding interactions (Figure 6A). Additionally, a high intermolecular binding energy value ($-9.27 \text{ kcal mol}^{-1}$) was exhibited by the MTSC ligand toward the 3hb5-oxidoreductase protein. The 3hb5-oxidoreductase protein was found to be effectively inhibited by the MTSC ligand, whereas the MTSC ligand has a high affinity energy toward speckle-type POZ protein (SPOP)-binding protein ($312.12 \text{ kcal mol}^{-1}$), which indicates that the MTSC ligand has a low inhibitory effect on SPOP. This molecular docking data showed that, in

contrast to SPOP-binding protein, MTSC can effectively bind to the 3hb5-oxidoreductase protein and may show considerable regulation on this target protein.

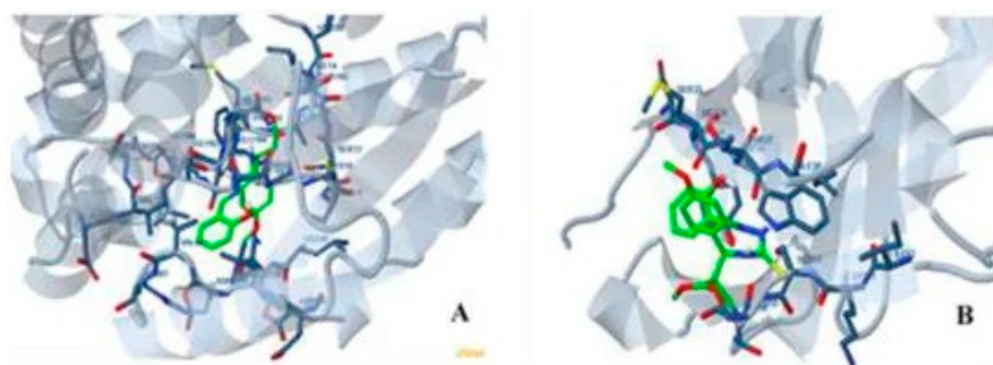


Figure 6. MTSC ligand 3D molecular docking against (A) 3hb5-oxidoreductase protein and (B) speckle-type POZ protein (SPOP)-binding protein.

In another study, Guin et al. reported 4-anisaldehyde thiosemicarbazone (4-HAntsc) and their Zn(II) and Cd(II) complexes, followed by density functional theory (DFT) calculations and molecular docking studies against the ATP-gated P2X7 ion channel (AGP2X7IC) and the human M1 muscarinic acetylcholine receptor (HM1CR) associated with Alzheimer's disease. In addition, the adsorption, distribution, metabolism, excretion and toxicity (ADMET) and drug-likeness properties of the ligand and its metal complexes were predicted. The ligand 4-HAntsc and its metal complexes $[\text{Zn}(4\text{-Antsc})_2(\text{SO}_4)]$ and $[\text{Cd}(4\text{-HAnTsc})_2\text{Cl}_2]$ exhibited biological activity through the participation of O, N and S atoms in binding. The non-toxic behavior of the complexes is confirmed by ADMET studies. Molecular docking studies show that the Zn(II) complex with a binding energy of $-52 \text{ kcal mol}^{-1}$ inhibits the HM1CR, which is one of the possible protein receptors associated with Alzheimer's disease, better than the Cd(II) complex with a binding energy of $-50 \text{ kcal mol}^{-1}$. Molecular docking studies also indicate that the Zn(II) and Cd(II) complexes have stronger binding to Alzheimer's proteins than the standard drugs Donepezil and Rivastigmine [21]. Manakkadan et al. reported three Cu(II) complexes (CTS1–CTS3) of acenaphthene quinone TSC. It was revealed by docking studies on the EGFR protein (PDB ID: 5EDQ) that CTS2 has the highest affinity, with a docking energy of $-7.41 \text{ kcal mol}^{-1}$. DFT studies revealed that CTS3 exhibits higher structural stability, indicated by a band gap of 0.10634 eV, while CTS2 demonstrates stronger biological activity due to a lower ω value of 0.5864 eV. Swiss-ADME studies indicate that satisfactory lipophilicity ($\text{LogP} > 5$) values are exhibited by all three complexes, suggesting their potential as effective oral drug candidates. The greatest cytotoxic activity against (cervical) (HeLa), lung (A549), and breast (MCF-7) cancer cell lines was demonstrated by CTS2, as revealed by MTT assay, with IC_{50} values of 19.6, 43.9 and 11.5 μM , respectively. In contrast, CTS2 has the lowest cytotoxicity against normal (Vero) kidney epithelial cells, with an IC_{50} value of 79.7 μM [22]. Souza et al. found Co(III) and Mn(II) of 2-acetylpyridine-*N*(4)-methylthiosemicarbazone ligand (Hatc-Me), a monomer complex $[\text{CuCl}(\text{atc-Me})]$ and a novel dinuclear complex $[\{\text{Cu}(\mu\text{-atc-Me})\}_2\mu\text{-SO}_4]$. Intermolecular interactions in the complexes were further confirmed by Hirshfeld surface and energy framework analyses. Six different strains of mycobacteria, including Mycobacterium tuberculosis, were used to test the biological activity of the Cu(II) salts, the free ligand, and its Cu(II) complexes. The complexes were found to exhibit antibacterial activity against *M. avium* and *M. tuberculosis* within the range of 6.12–12.73 μM . Molecular docking analysis was performed, yielding highly favorable binding energies of -14.03 and $-11.11 \text{ kcal mol}^{-1}$ for $[\{\text{Cu}(\mu\text{-atc-Me})\}_2\mu\text{-SO}_4]$ against *M. avium* and *M. tuberculosis*, respectively. The in silico studies demonstrate that

the complexes could be used as potential candidates in the development of novel antimicrobial drugs [23]. In another study, Khan et al. reported mixed ligand complexes of Zn(II), Co(II), Fe(II) and Cu(II) with 2-butanone TSC and 1, 10 phenanthroline. The bioactivity score prediction, toxicity potential and drug-likeness of the complexes were also assessed through computational studies using different drug filters. Only the Cu complex displayed one Lipinski's violation, while all the other complexes showed no Veber's violations. Positive bioactivity as enzyme inhibitors was exhibited by some of the compounds. The complexes were subjected to molecular docking against topoisomerase II (Topo II) and ribonucleotide diphosphate reductase (RR), and for the determination of minimum binding energies (kcal mol^{-1}). The Fe complex has the lowest binding energy of $99.8349 \text{ kcal mol}^{-1}$ when docked with RR, while the Cu complex has the highest affinity for Topo II with a binding energy of $-101.13 \text{ kcal mol}^{-1}$. The ligand has potential anticancer activity against the MDA-MB-231 cell line, the results of which are comparable to the standard drugs doxorubicin HCl and tetracycline using the MTT assay. The complexes also have antibacterial activity against *S. aureus* and *E. coli*. The highest cytotoxic activity toward MDA cells and mild antibacterial effects against *S. aureus* were demonstrated by the Cu(II) complex [24]. El-Sayed et al. reported Fe(II), Mn(II) and Ni(II) complexes of (E)-2-(4-hydroxybenzylidene) hydrazine-1-carbothioamide (Schiff base-TSC). Significant reactivity and favorable electronic transitions were exhibited by the Ni(II) complex, as demonstrated by DFT calculations with an energy gap of 1.190 eV. Furthermore, the stability of the complex was evaluated using another set of calculated quantum chemical parameters. In silico studies indicated that the designed metal complexes have significant inhibition activity against *Bacillus cereus*, particularly $[\text{NiL}_2\text{Cl}_2]$, which showed a higher binding affinity of $-7.1 \text{ kcal mol}^{-1}$. Further in silico studies were performed on the Gram-positive bacterial strain *S. aureus*, and the results supported the experimental findings by showing increased inhibition in the presence of the MnL_2Cl_2 complex. Based on the calculated binding affinity, a more stable Mn(II) conformer ($-9.4 \text{ kcal mol}^{-1}$) was determined by docking studies. Comparison with experimental results indicated that MnL_2Cl_2 has lower MIC values ($\leq 16\text{--}32 \text{ }\mu\text{g/mL}$) against *Pneumonia* and *B. cereus*. The antioxidant activity of the complexes was also evaluated, and significant free radical scavenging was observed. The IC_{50} values were found to be $38.33 \text{ }\mu\text{g/mL}$ for FeL_2Cl_2 , $27.35 \text{ }\mu\text{g/mL}$ for NiL_2Cl_2 , and $34.79 \text{ }\mu\text{g/mL}$ for MnL_2Cl_2 , while ascorbic acid has $22.35 \text{ }\mu\text{g/mL}$. Insights from these biological studies may provide a framework for the future evaluation of other metal series, aiming to identify potent inhibitors for therapeutic applications [25]. In a previous study, the impact of the metal ion and coordination on stabilization interactions in the crystal structure was investigated using Hirshfeld surface analysis. Figure 7 depicts the Hirshfeld surface of Pyridoxal-thiosemicarbazone (PLTSC) [26].

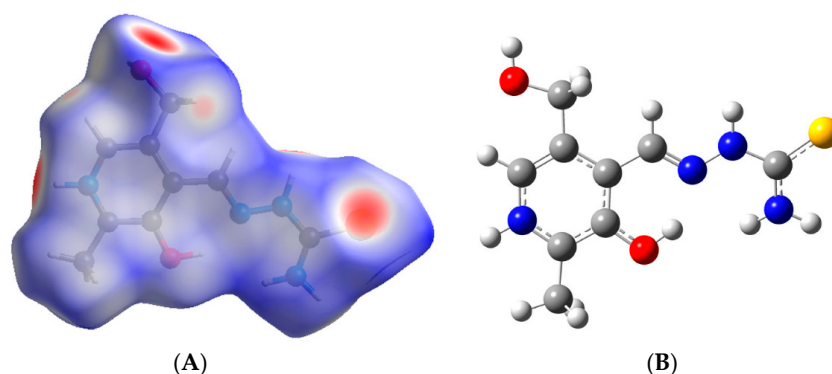


Figure 7. The Hirshfeld surface. (A) PLTSC structure optimized at the B3LYP/6-31+G(d,p) theory level. (B) Sulfur, yellow; nitrogen, blue; oxygen, red; carbon, grey; hydrogen, white.

4. Mechanistic Insight of TSCs

4.1. Inhibition of DNA Interactions and Topo II

DNA decatenation is caused by the enzyme called topoisomerase, which is present in eukaryotic cells and is required for the replication of DNA. During replication, it also stops supercoiling [27,28]. Topo II plays a crucial role in cell division and is abundantly present in cancerous cells. TSCs are potent anticancer drugs that effectively inhibit the activity of Topo II. Researchers investigated the correlation between the performance of ^{64}Cu -labeled thiosemicarbazide complexes in vitro and in vivo, and Topo II activity expression [29]. Four nonane thiosemicarbazide ligands (^4N -azobicyclo [3.2.2]) were synthesized and radiolabelled with ^{64}Cu , resulting in the production of lipophilic cations (Figure 8). Out of four ligands, three were shown to have superior growth inhibition properties in HT29 cells, with an IC_{50} value of $0.004 \mu\text{mol/L}$, when compared to non-radioactive copper. Numerous nitrogen-based heterocycles containing tridentate TSCs have been explored. It has been found that a ligand with a quinoline group exhibits high cytotoxicity and the capacity to inhibit the activity of Topo-II [30]. A subsequent study revealed that the Cu complexes of the same ligand inhibited Topo-II [31]. Compared to the uncomplexed ligand, Cu complexes have better growth inhibitory effect and lower IC_{50} values against cancer cells than the previously demonstrated Topo-II inhibitors [32]. The antitumor activity of 1,2 naphthoquinone-2-thiosemicarbazone and its Ni(II), Cu(II) and Pd(II) complexes was tested against the breast cancer (MCF-7) cell line, demonstrating promising antitumor properties. Based on IC_{50} values, the Ni complex has been found to be very effective [33].

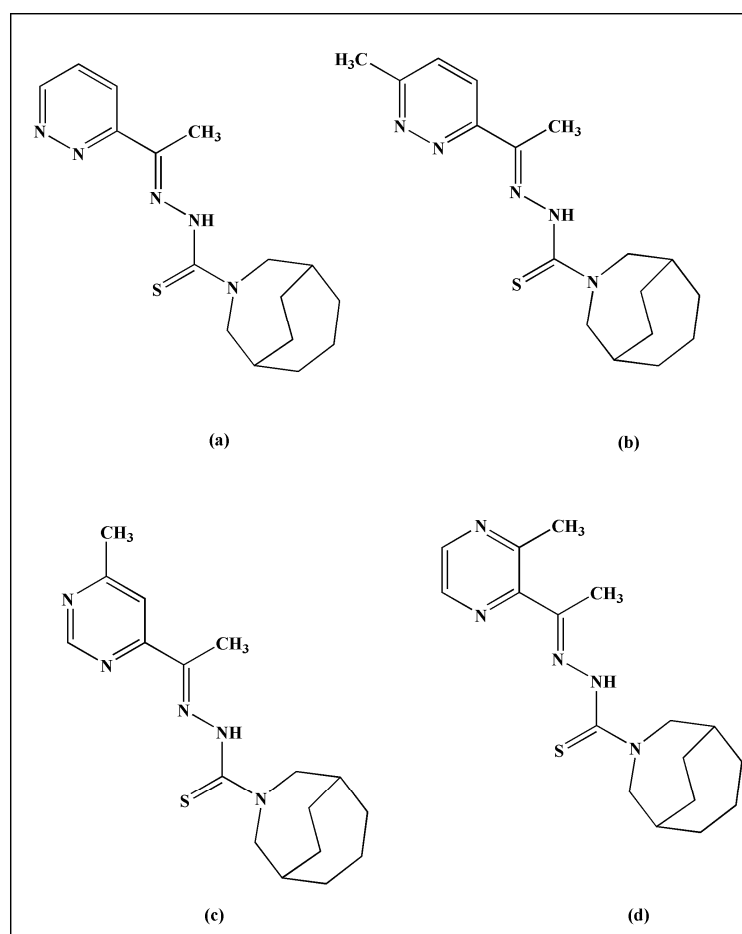


Figure 8. ^4N -azobicyclo [3.2.2] nonane TSC ligands: (a) EPH142 (b) EPH143 (c) EPH144 (d) EPH270.

4.2. ROS Generation

Complexes of redox metals have the ability to generate ROS [2]. The biological activity of $[\text{Cu}(\text{L})_2(\text{dca})](\text{ClO}_4)$ and $[\text{Cu}(\text{L})_2(\text{pz})](\text{ClO}_4)$ complexes, where L = 2-formylpyridine thiosemicarbazone, dca = dicyanamide and pz = pyrazine on DNA has been evaluated. These complexes were observed to induce both single- and double-strand DNA breaks [34]. Cu is an essential micronutrient that plays a crucial role in biological processes, including modulation of angiogenesis [35,36], redox regulation and cellular trafficking [37,38]. Four new metal complexes of TSC— $[\text{Cu}(\text{Am}_4\text{M})(\text{OAc})]\cdot\text{H}_2\text{O}$ (1), $[\text{Zn}_2(\text{Am}_4\text{M})_2(\text{OAc})_2]\cdot 2\text{MeOH}$ (2), $[\text{Zn}_2(\text{Am}_4\text{M})_2\text{Br}_2]$ (3) and $[\text{Zn}(\text{HAM}_4\text{M})\text{Cl}_2]$ (4) where $\text{HAM}_4\text{M} = (\text{Z})$ -2 (amino(pyridin-2-yl) methylene)-N-methylhydrazinecarbothioamide have been reported and evaluated towards HepG-2 cells. The IC_{50} value of complex-1 ($11.2 \pm 0.9 \mu\text{M}$) against HepG-2 cells is approximately half that observed in human hepatic cell lines LO-2, indicating a decrease in adverse effects on liver cells. It has been observed that complex1 exhibits greater inhibition on HepG-2 cell viability compared to cis-platin ($\text{IC}_{50} = 25 \pm 3.1 \mu\text{M}$), indicating that it may be an effective anticancer drug. The analysis of flow cytometry and fluorescence microscopy has revealed that complex-1 cannot inhibit the viability of HepG-2 cells and promote cell death. Various indicators, including comet assay, ROS generation, DNA cleavage and the analysis of cell cycle, indicated that the anticancer mechanism of complex-1 in HepG-2 cells may involve the apoptosis pathway triggered by ROS [39]. Complexes 1–4 exhibit varied coordination geometries under similar synthetic conditions, influenced by factors such as the metal ion's properties (including coordination numbers and ionic radius) and the presence of different counter anions (OAc^- , Br^- , Cl^-) [2].

4.3. Multidrug Resistance Protein (MDR1) Inhibition

One of the biggest obstacles and clinical challenges in the development of anti-cancer medications is multidrug resistance. Tumor cells can develop multidrug resistance, making them resistant to other types of anticancer drugs to which they have not been previously treated [40]. The antiproliferative effect of Pd complexes with phenanthrenequinone thiosemicarbazone in breast cancer cells and normal cells has been investigated. The findings indicated that the complex demonstrated a strong anti-neoplastic effect, selectively targeting tumor cells, particularly effective against breast cancer cells that have developed resistance to these drugs [41].

5. Future Prospects

Over the next decade, advanced technologies and algorithms are expected to be developed through continued advancements in computer-aided drug design and discovery. The identification of potential drug candidates and the prediction of their toxicity, efficacy and pharmacokinetics are expected to be increasingly supported by AI and machine learning approaches. The ability to accurately predict the binding affinity of a potential drug molecule to its target protein is one of the major obstacles that researchers are facing. Despite significant recent advancements in computational methods, further research is required to develop more accurate models and algorithms for predicting binding affinities. The use of extensive datasets and the integration of complex molecular interactions are expected to be required. The in vivo behavior of drug molecules is another challenge to predict accurately. In silico models are valuable for predicting pharmacokinetics and toxicity; however, there is a necessity for more accurate models that account for the complex interactions between drug molecules, targets and biological systems. To overcome existing challenges, it is essential for researchers to develop advanced algorithms and computational tools that successfully merge machine learning, molecular modeling and big data analytics. Furthermore, a comprehensive understanding of drug design and discovery depends on

effective collaboration among multiple disciplines, such as biology, chemistry, computer science and medicine. Further research and development will be required to fully exploit the opportunities offered by these technologies and to overcome the challenges associated with drug discovery and development [42].

6. Conclusions

TSC complexes have significantly higher biological activity compared to parent TSCs. These complexes have potential applications in treating various fatal diseases. This review provides TSC complexes and their biological applications. Moreover, these computational techniques enable researchers to examine electronic structures and spectroscopic characteristics, which are crucial for establishing structure–activity relationships (SARs) and understanding reactivity patterns. The gap between experimental research and theoretical understanding is bridged by computational studies, enabling the behavior of metal complexes in various biological and chemical systems to be predicted and optimized. The design and development of more effective compounds for various applications is made easier by this approach. This might be a big advantage for the future advancement of adaptive molecules for a variety of activities.

Author Contributions: Conceptualization, S.J. and K.H.; resources, S.J.; data curation, K.H., T.K. and S.J.; writing—original draft preparation, K.H. and S.J.; writing—review and editing, K.H., S., P.M., E.V., T.K. and S.J.; visualization, K.H., T.K. and S.J.; supervision, S.J. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Acknowledgments: The authors are thankful to the President and Principal, Isabella Thoburn College, Lucknow for extending the necessary facilities and cooperation to carry out the work.

Conflicts of Interest: The authors declare no conflicts of interest.

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