INTERNATIONAL JOURNAL FOR INNOVATIVE RESEARCH IN MULTIDISCIPLINARY FIELD
ISSN(O): 2455-0620 [Impact Factor: 7.581]
Monthly, Peer-Reviewed, Refereed, Indexed Journal with IC Value : 86.87
Volume - 9, Issue - 9, September- 2023 Publication Date: 30/09/2023

DOIs:10.2015/IJIRMF/202309020 --:-- Research Paper / Article / Review

TRANSITION METAL COMPLEX DERIVATIVES OF THIOSEMICARBAZONE AS MULTI TARGET DRUGS

[1]Dr. B. Karpagam [2]Dr. G. Rajagopal
[1]Department of Chemistry, St. Michael College of Engineering and Technology, Kalayarkoil 630551, Sivaganga District, Tamilnadu 630551, India
[2]PG & Research Department of Chemistry, Chikkanna Government Arts College, Tiruppur-641 602, India
Email: [1]karpagamsentil@gmail.com

Abstract: *Schiff-base compounds have been used as fine chemicals and drug delivery systems. The azomethine group (-C=N-), which is frequently found in Schiff's bases, is produced by condensing primary amines with active carbonyls. Thiosemicarbazones (hydrazine carbothioamides) are a class of compounds with favourable biological activity. The fascinating notion that the biological activity may also depend on the extra functional groups that are not coupled to their "primary" metal ions is raised by the existence of these groups in the more pharmaceutically interesting thiosemicarbazone derivatives. It is well known that the biological activity of hydrazone compounds and the existence of the active (-CO-NHN=C-) pharmacophore are connected. Hydrazone compounds are a significant class of molecules in medical and pharmaceutical chemistry with diverse biological applications.*

Key words: *Thiosemicarbazones, biological activity, Coordination behaviour.*

1. INTRODUCTION:

Metal complexes relevant to synthetic and biological oxygen carriers are designed in large part using Schiff's base complexes [1–3]. In addition to serving as ligands for the complexation of metal ions, Schiff bases are significant intermediates in the production of several bioactive chemicals, such as ß-lactams [4]. Because of their significant features, such as their capacity to interact reversibly with oxygen redox systems in biological systems and the oxidation of DNA, Schiff bases and their complexes are extensively investigated. In the realm of coordination chemistry, Schiff bases are frequently utilized as chelating ligands, and their metal complexes have long piqued the curiosity of scientists. The critical function N and S atoms play in the coordination of metals at the atomic level is well-known.

2. THIOSEMICARBAZONES - VERSATILE LIGANDS:

Thio-semi carbazones act as ligands because;

- They have better co-ordination tendency.
- They form more stable complexes.
- They have better selectivity.
- They may form macrocyclic ligands.
- They have the ability to produce some new and unique complexes with enhanced biological and analytical properties.

3. THIOSEMICARBAZONES IN THE BIOLOGICAL FIELD - A SURVEY:

As a result of their diverse biological activity and potential for use as medications, thiosemicarbazones and their metal complexes have been extensively researched for nearly 50 years [5]. Thiosemicarbazones and their metal complexes have been thoroughly researched as a result of the interest they generate due to a variety of biological features including anticancer antitumor [6], antifungal [7], antibacterial [8], antimalarial, anti-filarial, antiviral, and anti-HIV activity. Recent research has focused heavily on the hypoxia selectivity of some copper bis(thiosemicarbazones) and how to employ them to transport radioactive copper isotopes to tumors or leucocytes. The substituents on the carbon backbone have a significant influence on the hypoxia selectivity. The biologically active thiosemicarbazone molecules were planar and had either a pyridine ring or a NNS tridentate system, according to earlier investigations on the biological characteristics of thiosemicarbazones and their metal complexes. It is now well accepted that biological

activity depends on the parent ketone or aldehyde, and that the biological activity is significantly increased by the presence of a bulky group at the terminal nitrogen [9].

According to studies on N (4) substituted thiosemicarbazones, the presence of bulky groups at the N (4) position of the thiosemicarbazone moiety significantly increases biological activity [10]. This additional potential bonding site also helps. It is thought that the reason thiosemicarbazone molecules are active is because they can chelate with traces of metals in biological systems. Coordination modifies the lipophilicity, which regulates the rate of entry into the cell, and may lessen some adverse effects. Thiosemicarbazones have been shown to inhibit the enzyme ribonucleoside diphosphate reductase, which is necessary for DNA synthesis in mammalian cells. This inhibition may occur either through chelation with an iron ion required by the enzyme or because the target enzyme interacts with a preformed metal chelate of the inhibitor [11]. Metal complexes of TSCs have attracted attention as improved drugs because of the following advantages:

- The long-term side effects of therapeutic agents can be avoided since metal complexes could
- break down and the metal ion may interact with the organism.
- Metal complexes may act as a vehicle for the activation of ligand, which is the principle
- cytotoxic agent.
- The complexation with metal ion may lead to reduction of drug resistance by several orders
- of magnitude
- A large number of such complexes involve biologically essential elements such as Copper
- and Zinc.

4. ANTITUMOR ACTIVITY:

Thiosemicarbazone chemicals are being researched for use in treating cancer, which is one of their most promising applications. Their anticancer action is very differentiated and highly reliant on the cellular types of the tumor [12]. Because it indicates selectivity, this property makes the entire class of chemicals extremely fascinating. The fact that their activity is unquestionably attributed to more than one target in the cell machinery makes it challenging to extrapolate general information from the literature that is applicable to the entire class of chemicals. However, the presence of a metal ion nearly always boosts the activity of the organic parent chemicals or helps to lessen their negative effects [13]. Currently, the main known effects connected to their anticancer activity are, in order of discovery, the inhibition of ribonucleotide reductase (RR), the production of reactive oxygen species (ROS), the disruption of mitochondria, and, more recently, the inhibition of a multidrug resistance protein (MDR1) [14].

5. HYPOXIA AND MULTIDRUG RESISTANCE:

Thiosemicarbazone metal complexes are currently gaining a lot of attention for their usage as carriers for radiotracers like 64Cu. In solid cancers with poor blood perfusion, this method is especially helpful. When a tumor outgrows its vascular supply, hypoxia frequently results, and cells naturally adjust by increasing the production of many proteins that aid in their survival [15]. The proteins expressed under these conditions block apoptosis and promote the development of metastatic disease. Normally, cells in this situation reduce the rate of growth and increase the formation of new vasculature. Any treatment is less effective because the hypoxic cells receive insufficient blood flow and oxygen. Researchers have been able to create compounds that accumulate with an inverse connection to O_2 partial pressure thanks to this hypoxic environment, initially to create imaging tools but more recently as a means of treating only malignant cells [16].

6. THIOSEMICARBAZONES – ENZYME MODELLING:

It has been discovered that the active centers of various metalloenzymes, including hydrogenases, xanthine oxidases, and nitrogenases, are composed of transition metal complexes of ligands with N/S donor centers [17]. Since nitrile hydratase also has a N_3S_2 donor set, bis (thiosemicarbazones) are utilized to create model complexes for the active sites of metalloenzymes with mixed N/S donor centers. Recent research has focused on the active sites of acetyl coenzyme synthase A and carbon monoxide hydrogenase [18].

7. RADIOLABELLING AND IMAGE SENSING:

Designing new imaging probes for biological targets that may be used in vivo with a variety of molecular imaging techniques to achieve research and therapeutic goals is of great interest. For therapeutic and imaging purposes, non-invasive methods like PET (positron emission tomography) and SPECT (single photon emission computerized tomography) can be used to track the in vivo distribution of radiolabeled metal complexes of interest [19]. Recent studies

have employed fluorescence microscopy to monitor the uptake of specific compounds in living cells. Fluorescence microscopy has been used to investigate the degree of zinc bis(thiosemicarbazones) complex absorption in human cancer cells as well as the location of the complex within the cell. Because they are luminous, bis(thiosemicarbonato) copper complexes [20] are discovered to be useful for radiolabeling. Therefore, by binding to amyloid - - plaques, the substances thought to be related with the disease, they are beneficial for diagnostic imaging of Alzheimer's disease.

8. METALLO – ELEMENTS UNDER INVESTIGATION:

The complexation behavior of thiosemicarbazones with various first series transition metal ions is under investigation.

- **COPPER:** Copper typically has an oxidation state of +2, and when it forms complexes with different ligands, the ligand field separates the d-orbital, electronic configuration d9. They easily combine tetrahedral, square planar, trigonal bipyramidal, square pyramidal, octahedral, and distorted octahedral geometries to generate coordination complexes including coordination numbers 4, 5, and 6.
- **COBALT** :Salts of Co (II) are more stable because they are not easily oxidized to Co (III) state, and cobalt exhibits two significant oxidation states as +2 and +3. However, Co^{2+} is rather quickly converted to Co^{3+} in basic solutions. When an element is subjected to complex formation in both of its oxidation states, it is typically discovered that the higher oxidation state's overall formation constant is larger, making reduction more challenging.
- **NICKEL:** The first-row transition series includes Nickel. It has an electronic valence shell structure of d8. In the zero-oxidation state, nickel can form tetrahedral-shaped complexes that are remarkably stable. Due to the minor free energy differences between each stereochemical form, Ni (II) is noted for its ability to form six coordinate octahedral configurations, five coordinate square pyramidal or trigonal bipyramidal configurations, and four coordinate square planar or tetrahedral configurations.
- **ZINC:** Zn (II) ion complexes are of biological significance since this metal is a component of numerous biomolecules. Because zinc (II) behaves as a Lewis acid, it can be an effective catalyst for hydrolysis processes. The Zn (II) ion has a d10 outer electronic configuration, and the bivalent state is quite stable because of the filled sublevel. It exhibits significant flexibility in the structure, manner of coordination, and quantity of coordinated complexes.
- **VANADIUM:** Vanadium can exist in various oxidation states; the +3, +4, and +5 oxidation states are frequently observed in naturally occurring vanadium compounds. Because of the typical five coordinate square pyramidal or six coordinate distorted octahedral geometries used by vanadium complexes, trigonal bipyramidal stereochemistry is not a possibility due to electronic and steric limitations**.**

9. CONCLUSION:

These thiosemicarbazones are used to treat rheumatoid arthritis, TB, leprosy, and psoriasis because research has shown that they have antibacterial, antiviral, and antiproliferative characteristics. HSV and HIV infections were selectively inhibited by certain thiosemicarbazones. In clinical use, oral administration of the majority of thiosemicarbazones is challenging due to their severe insolubility in water. While the acidity of the 2NH enables the ligand to be anionic or neutral, the type of the substituent attached at 4N affects the biological activity. It is discovered that uncombined thiosemicarbazones are less active than transition metal complexes. They display a range of denticity and are adaptable with appropriate substitution. Thiosemicarbazones' stereochemistry is determined by a number of variables, including the preparation circumstances, the presence of extra bonding sites in the ligand moiety, and the charge of the ligand. The resultant compounds showed a wide variety of stereo chemistry, had biomimetic properties, and might be used as sensors.

REFERENCES:

1. A. Asiri, A. Al-Youbi, S.Khan, M.Tahir (**2011**): 2-[(E)-(3,4-Dimethylisoxazol-5-yl)imino-methyl] phenol Acta Crystallogr Sect E66 0773-0774.
2. Nihad I. Taha, Nashwan O. Tapabashi, Marwa (**2018**) Green Synthesis of New Tetra Schiff Bases and Bis-Azo Bis-Schiff Bases Derived from 2,6-Diaminopyridine as Promising Photosensitizers Int. J. Org. Chem., 08 309-318.
3. A.H. Kadhum, A. Mohamad, A.A. Al-Amiery, M.S.Takriff (**2011**) Anticorrosion and antibacterial effects of new Schiff base derived from hydrazine Molecules 16 6969.

4. F. Aydogan, N. Öcal, Z.Turgut, C.Yolacan (2011): Synthesis, characterization and antibacterial investigation of divalent metal complexes of NO-donor ligand: {5-chloro-2-[(4-chlorobenzylidene)-amino]phenyl}(phenyl)methanone Bull Korean Chem Soc 22 476-480.
5. S. Park, V.K.Mathur, (**1998**): Syntheses, solubilities and oxygen absorption properties of new cobalt(II) Schiff-base complexes Polyhedron 17 325-330.
6. L.F. Landy, (ed) (**1989**) The chemistry of macrocyclic ligand complexes. Cambridge University Press, Cambridge.
7. Emad Yousif, Ahmed Majeed, Khulood Al-Sammarrae (**2017**): Metal complexes of Schiff base: Preparation, characterization and antibacterial activity Arab. J. Chem 10 S1639-1644.
8. D.P. Yang, H.F. Ji, G.Y. Tang, W. Ren, H.Y. Zhang, (**2007**): How many drugs are catecholics Molecules 12 878-884.
9. S.J. Berners, (**2007**) Metals in medicine. Keynote Lectures, Bio Inorg Chem 12 S7-14.
10. Mario Prejano, Marta Erminia Alberto, Nino Toscano (**2020**) The Effects of the Metal Ion Substitution into the Active Site of Metalloenzymes: A Theoretical Insight on Some Selected Cases catalysts, 10 (9) 1038-1044.
11. N. Raja, R. Ramesh, (**2010**) Mononuclear ruthenium (III) complexes containing chelating thiosemicarbazones: Synthesis, characterization and catalytic property Spectrochimica Acta Part A,75 713-718.
12. Fatima Kanso, Alia Khalil, Hiba Noureddine, Yolla El-Makhour (**2021**): Therapeutic perspective of thiosemicarbazones derivatives in inflammatory pathologies: A summary of in vitro/in vivo studies Int. Immunopharmacol. 96 107778-107783.
13. V. Philip, V. Suni, M.R.P. Kurup, M. Nethaji, (**2006**): Structural and spectral studies of nickel (II) complexes of di-2-pyridyl ketone N4, N4-(butane-1, 4-diyl) thiosemicarbazone Polyhedron 23(7) 1225-1233.
14. Zhang-Xu He 1, Jin-Ling Huo 1, Yun-Peng Gong, Qi An, Xin Zhang, (**2021**) Design, synthesis and biological evaluation of novel thiosemicarbazone-indole derivatives targeting prostate cancer cells Eur. J. Med. Chem 210 112970-112976.
15. W.-Hu, W. Zhou, C.-Xia, X. Wen, (**2006**) Synthesis and anticancer activity of thiosemicarbazones Bioorg. & Med. Chem. Lett. 16 2213-2216.
16. Calonghi N. Boga C. Nitti P. Telese D. Bordoni S. Farruggia G. Asaro F. Grandi M. Zalambani C. Micheletti G. (**2022**) Effects of Regioisomerism on the Antiproliferative Activity of Hydroxystearic Acids on Human Cancer Cell Lines, Molecules, 27, 2396-2402.
17. S. Padhye, Z. Afrasiabi, E.Sinn, Fok, K. Mehta, N. Rath, (**2005**) Synthesis, Characterization and Cytotoxic Properties of Pd(II), Cd(II) and Hg(II) Complexes of 2-Amino-5- Chloro-Benzophenone-4-(H/Ph)-Thiosemicarbazones Inorg.Chem. 44 1154-1160.
18. M.A. AI, A.H. Mirza, RJ. Butcher, K.A. Crouse, (**2006**) The Preparation, Characterization and Biological Activity of Palladium (II) and Platinum (II) Complexes of Tridentate NNS Ligands Derived from S-methyl- and S-benzyldithiocarbazates and the X-ray Crystal Structure of the [Pd(mpasme)Cl] Complex Transition Met.Chem. 31 79-87.
19. Xiaohua Jiang, Lauren A. Fielding, Hunter Davis, William Carroll, Edward C. Lisic Joseph E. Deweese, (**2023**) Inhibition of Topoisomerases by Metal Thiosemicarbazone Complexes Int. J. Mol. Sci., 24(15) 12010-12016.
20. Garima Matela (**2020**) Schiff Bases and Complexes: A Review on Anti-Cancer Activity J. Med. Chem 20(16) 1908-1917.