Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 7 Issue 11 November 2023

Research Article

Synthesis, Characterization and Anti-bacterial Activity of Co(II) and Ni(II) Complexes with a NSO Donating Site Schiff Base Ligand Derived from N-ethylhydrazinecarbothioamide and 5-bromo-2-hydroxy-3-methoxybenzaldehyde

Afnan Islam and Md Azharul Arafath*

Department of Chemistry, Shahjalal University of Science and Technology, Bangladesh

***Corresponding Author:** Md Azharul Arafath, Department of Chemistry, Shahjalal University of Science and Technology, Bangladesh.

Received: August 21, 2023

Published: October 06, 2023

Abstract

A NSO tridentate Schiff base ligand (E)-2-(5-bromo-2-hydroxy-3-methoxybenzylidene)-N-ethyledrazine-1-carbothioamide (L1) of a new carbothioamide has been synthesized. Co^{2+} and Ni^{2+} metal was introduced to tridentate Schiff base ligand to make coordination complexes. Square planar complex of Ni^{2+} and octahedral complex of Co^{2+} metal-ions were formed respectively and compounds Na [NiLCl] and Na $[CoL(OH_2)_2Cl]$ have been found under basic condition. Characterization of these compounds are done by on the basis of melting point, FT-IR spectroscopy and UV-Visible spectroscopy. As the new complexes possesses azomethine(=C=N−) group so they have potential biological activity. For antibacterial study the solution of complexes and ligand was applied against the bacteria *S. aureus* and *B. subtilis* to find out their inhibition with bacteria.

Keywords: Thiosemicarbazone; Schiff Base Ligand; Cobalt Complex; Nickel Complex; FT-IR Spectroscopy; UV-Visible Spectroscopy

Introduction

Schiff bases are important in organic synthesis and have variety of applications in various fields including medicine and material science. In honour of Hugo Schiff, who was the first person to successfully synthesized such chemical containing azomethines are commonly named as Schiff bases [1,2]. As part of his dissertation, he focused on the chemistry of aniline [3] while completing his education in Gottingen under Friedrich Wohler [3]. Thiosemicarbazones typically exist in the thioamido form when they are in the solid state. However, when they are in the solution state, they tend to exist as an equilibrium mixture of the thioamido and thioiminol forms. The pH of the medium that is being utilized for the reaction has an effect on the thioamido-thioiminol equilibrium. Both the neutral and the anionic forms of thiosemicarbazones are capable of binding to the centres of metal ions.The thiosemicarbazones of aromatic aldehydes and ketones form stable chelates with transition metal cations such as Co^{2+}, Ni^{2+} etc. and some p-block metal cations by utilizing their both the sulphur and azomethine nitrogen as donor atoms [4]. The chelated complexes that can form, such as Na $[CoL(H_2O)_2Cl]$, Na [NiLCl], etc. are also stable complexes. Aliphatic aldehydes are unstable and readily polymerize, whereas aromatic aldehydes, especially those with an effective conjugation system, can form stable Schiff bases [5] When working with aldehydes rather than ketones (carbonyl carbon), it is easier to produce Schiff base ligands [6]. Compared to Schiff bases containing alkyl substituents, those containing aryl substituents are significantly more stable and easier to synthesize [7]. Thiosemicarbazone has a great concern as a derivative of Schiff base. [3] The thiosemicarbazones are thiourea derivatives and are synthesized by the condensation of thiosemicarbazide with aliphatic or aromatic aldehydes or ketones in acidic medium [8]. Due to the fact that they are able to diffuse all the way through the semipermeable membrane of the cell lines, it has been demonstrated that they possess a wide variety of biological activities, some of which are anticancer [9], antitumor [10], antibacterial [11,12] , antiviral [13,14], antimalarial [15] and antifungal [16]. When compared to the ligand on its own, the metal complexes have a greater degree of lipophilicity, which may be responsible for the heightened impact. The complexes' activi-

ties are amplified when coordination sites are present inside the complexes. These complexes have the potential to find additional applications in the treatment of incurable diseases such as hepatitis, AIDS, and other similar conditions and in catalytic activity [17,18]. As a result of this, there has been a lot of focus placed on the structural and chemical features of thiosemicarbazones and the metal complexes that they form [19-23]. Also, the pharmacological activity is correlated to the fact that they can reduce oxygen. It has been discovered that the biological activity is dependent on the parent aldehyde or ketone [24–26], and that it significantly increases when bulky groups are present in the N4 position [27]. When compared to the free thiosemicarbazone ligand, the activities that can be observed in metal complexes of thiosemicarbazones are frequently superior. Their activity against fatal diseases like cancer and aids encouraged us to synthesize such type of novel Schiff base compound base ligand (E)-2-(5-bromo-2-hydroxy-3-methoxybenzylidene)-N-ethyledrazine-1-carbothioamide (L) and their complexes with $Ni^{2+}$and Co^{2+} metal ions Na [NiLCl] and Na $[CoL(OH_2)_2Cl]$ respectively. In this report we've tried to study and report their biological activity and theoretical study.

Experimental

Materials and Methods

Materials

The chemicals which were used 5-bromo-2-hydroxy-3-methoxybenzaldehyde, Ethylisothiocyanate, Hydrazine hydrate, $[Co(Cl)_2.]6H_2O$, $[Ni(Cl)_2].6H_2O$ were obtained from Sigma-Aldrich and Merck chemical company. Other chemicals used for the synthetic process NaOH, Glacial acetic acid was used without further purification and also purchased from chemicals supplier company. The solvents Diethyl-ether, Ethanol, Methanol, DMSO, *n*-hexane etc. were used to carry the reaction in research project purchased from Merck compony.

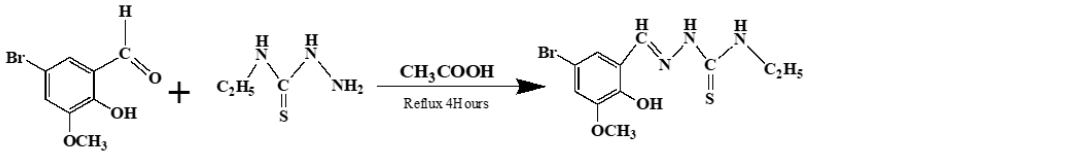
Methods

The IR spectrums were recorded by FTIR spectrophotometer, IR Prestige-21, Shimadzu Corporation, Japan, at department of chemistry, Shahjalal university of Science and Technology, Bangladesh using KBr as background. The Spectra were recorded from 4000 cm^{-1} to 400 cm^{-1} with a resolution of 8 Cm^{-1}. The UV-visible spectra were recorded on UV-visible Spectrophotometer (UV-1900, Shimadzu) in DMSO solvent. Gallenkamp electro thermal melting point apparatus was used to record the melting point of the ligand and the complexes. The heating was done carefully to ensure a steady rise of temperature.

Synthesis of ligand and complexes

Synthesis of ligand (L1)

About 1.0 gm (4 mmol) of 5-bromo-2-hydroxy-3-methoxybenzaldehyde was dissolved in 10 ml methanol, 0.5 ml of glacial acetic acid was added and refluxed for 30 min. Then 0.476 gm (4 mmol) of N-ethylhydrazinecarbothioamide in 10 ml methanol was dissolved and added dropwise with stirring with the aldehyde solution. The resulting light-yellow solution was refluxed for 4 hours with continuous stirring. Yellowish precipitate was formed. It was then allowed to dry in a desiccator. Physical state: Crystalline solid; color. Yellow; M.P: 161-165 °C.



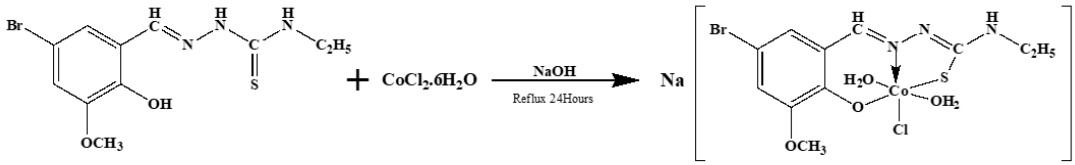
Scheme 1: The scheme shows the rout of synthesis of (E)-2-(5-bromo-2-hydroxy-3-methoxy benzylidene) -N-ethyledrazine-1-carbothioamide.

Synthesis of Na [CoL(H_2O)$_2$Cl]

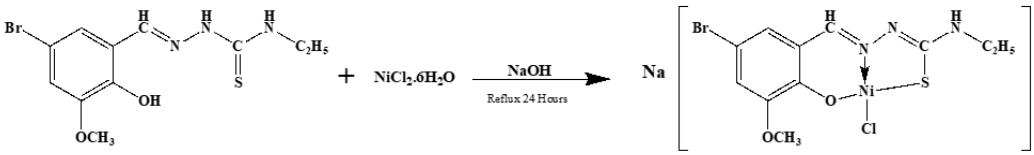
About 0.3 mmol (0.096 gm) of the ligand was dissolved in 20 ml methanol and 0.2 mmol of NaOH in 10 ml methanol was also added into it and the solution was refluxed for 30 minutes. The color of solution turned to yellow. A solution of 0.3 mmol (0.071g) of $Co(Cl)_2.6H_2O$ in 10 ml methanol was dissolved added dropwise with stirring to the ligand solution. The resulting solution was turned to deep brown. The resultant solution was refluxed for 24 hours. A deep brown precipitate of metal complex formed and filtered it out. The crude products were washed with methanol and *n*-hexane then purified and collected. Color: Chocolate brown. Physical State: powder Melting Point: >300 °C.

Synthesis of Na [NiL(Cl)]

About 0.2 mmol (0.064 gm) of the ligand was dissolved in 20 ml methanol. Then 0.2 mmol of NaOH in 10 ml methanol was also added into it and the solution refluxed for 30 minutes. The solution was turned to yellow. A solution of 0.2 mmol (0.0259 gm) of $Ni(Cl)_2.6H_2O$ in 15 ml methanol was dissolved and added dropwise with stirring to the ligand solution. The solution color was changed to deep yellow gradually. The resulting solution was refluxed for 24 hours with stirring. Yellowish precipitate of metal complex was formed. The product was filtered off and washed with methanol and *n*-hexane. The crude product was purified and collected. Color: Yellow. Physical State: Powder. Melting Point: >300 °C.



Scheme 2: The reaction scheme for the synthesis of Na[CoL(H_2O)$_2$Cl] metal complex.



Scheme 3: The reaction scheme for the synthesis of Na[NiL(Cl)] metal complex.

IR spectra

The FTIR spectrum is very important to find out whether the compound is formed or not; or it have any impurities. The broad band in the 3317 cm^{-1}in the spectrum of ligand (L) and 3143 cm^{-1} due to N-H and O-H vibrations respectively. The Imine bond (=C=N-) peak which is very significant to identify the Schiff base appeared at 1612 cm^{-1}. The formation of metal complexes by the ligand and metal salts were indicated by some noticeable changes in the IR frequencies of -OH, C=S and C=N vibrations. In the spectrum of the free ligand the O-H absorption was at 3143 cm^{-1} which was found absent in the frequency of the nickel complex but a broad peak was found in the spectrum of cobalt complex due to its octahedral structure. Most likely due to oxygen metal (O-M) bonding. This indicates the coordination of phenolic oxygen with the metal ions for all complexes of Cobalt and Nickel **[28]**. The other important observation is the shift in the C=S vibration lower by 40-60 cm^{-1} in the complexes **[29]** due to bonding to metal with lower frequencies than ligand at 1161cm^{-1}.The C=N vibration at 1612 cm^{-1} in the free ligand is shifted to lower frequencies for the complexes. The frequency of C=N to 1597 cm^{-1} and 1612 cm^{-1} for cobalt and nickel complexes **[30–32]**.

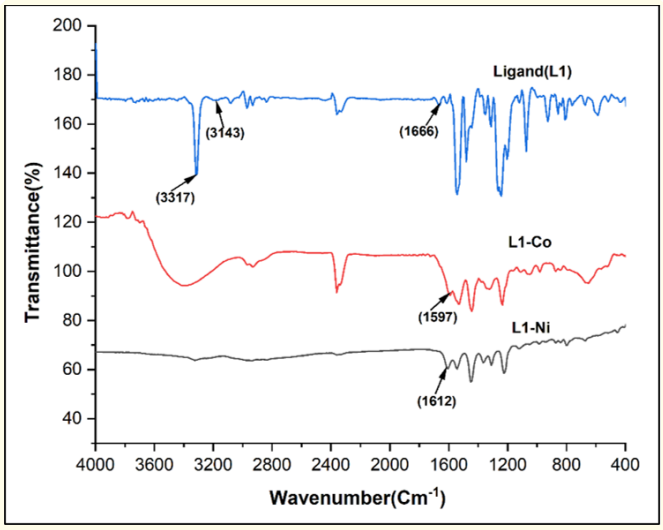


Figure 1: FT-IR spectra showing differences between ligand (L) and Metal complexes.

UV-visible spectra

The UV-visible spectra (Figure) presents important information about complexes with comparison to ligand. The ligand only itself shows intense broad band at 355 ± 5 nm with a small shoulder at 265 nm for n→π* and π→π* transitions respectively of the azomethine C=N bond [33]. The spectra of complexes show intense broad band at 400 ± 10 nm due to metal to ligand charge transfer transition [34-35]. The π→π* transition for the azomethine C=N of the complexes found at lower energy at 310 ± 10 nm, the π→π* transition due to the aromatic ring [36,37] appears at higher energy and exhibit an intense broad band in the region of 255 ± 5 nm.

Compound	ν (N-H) /Cm^{-1}	ν (O-H) /Cm^{-1}	ν (-CH3) /Cm^{-1}	ν (C=N) /Cm^{-1}	ν (C=C Ar.) /Cm^{-1}	ν (CH3 bend) /Cm^{-1}	ν (C=S) /Cm^{-1}	ν (C-N) /Cm^{-1}	ν (N-N) /Cm^{-1}	ν (C-S) /Cm^{-1}
N-ethyldrazine Carbothioamide	3348	---			1543	---	1273	1087	1087	---
Ligand(L1)	3317	3143	2970	1666	1543	1442	1203	1072	1118	---
[CoL(OH)$_2$Cl]	---	3414	---	1597	1631	1597	1035	1165	1165	650
[NiL(Cl)]	3780	---	---	1612	1450	---	1118	1311	979	671

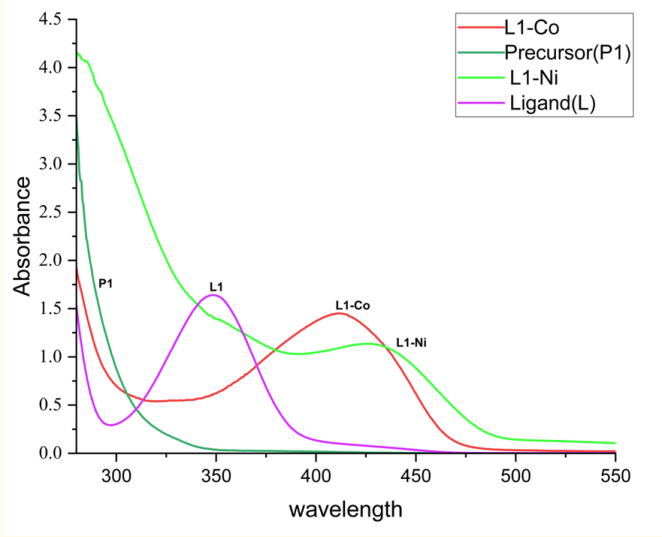


Figure 2: UV-Vis spectra of Ligand (L1), precursor and metal complexes.

Melting point

The melting point of aldehyde is (125-127)^{0}C and N-ethylhydrazinecarbothioamide is observed between (200-215)^{0}C but the Schiff base ligand melting point is between (161-165)^{0}C. So, a new product could be formed. Both Complexes Na [CoL(OH$_2$)$_2$Cl] and Na [NiL] have the melting point between (310-325)^{0}C.

Solubility and stability

Schiff bases having aryl groups can be synthesized more stable and easily due to the electron addition of the imine bond through ring conjugation, while those containing alkyl substituents are relatively unstable, synthesized in a long time, and polymerization is observed. As our carbothioamide has ethyl groups which is small and less bulky so our ligand is not very much stable and ligand is soluble I almost all solvent but the complexes are very stable they have fond only soluble in DMSO. The UV data of complexes also taken by dissolving them in DMSO (Di-methyl sulfoxide) with

two hours interval and they are UV spectrum was same like before which indicates the complexes are very stable.

Solvent	DMSO	Methanol	Hexane	Diethyl ether
Carbothioamide	✓	✓	✗	✓
Ligand(L1)	✓	✓	✗	✓
(L1-Co)	✓	✗	✗	✗
(L1-Ni)	✓	✗	✗	✗

Table 2: Solubility of synthesized products.

Antibacterial activity

In agar well diffusion test, the visible of clear zone around the disk containing Co and Ni complexes showing that the Co and Ni complexes possessed antibacterial activity which is able to inhibit the growth of only *Staphylococcus aureus* and *Bacillus subtilis*. The visible clear zone Created Co and Ni complexes by against *Staphylococcus aureus* and *Bacillus subtilis* is showed in Figure 3. For the bacterial inhibition test 100 ppm solution of each complex was made.

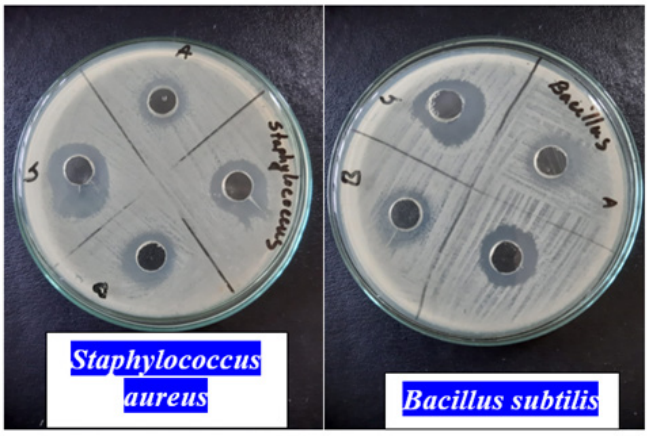


Figure 3: *In vitro* antibacterial activity of L1-Co and L1-Ni against two multidrug resistant bacterial superbugs.

Compound	*Staphylococcus aureus*	*Bacillus subtilis*
L1-Co	15	16
L1-Ni	16	17

Table 3: Zone Of inhibition (mm).

Bibliography

1. R H Holm., et al. "Metal Complexes of Schiff Bases and β-Ketoamines". in Progress in Inorganic Chemistry, F. A. Cotton, Ed. Hoboken, NJ, USA: John Wiley and Sons, Inc., (2007): 83-214.

2. P A Vigato and S Tamburini. "The challenge of cyclic and acyclic schiff bases and related derivatives". *Coordination Chemistry Reviews* 248.17-20 (2004): 1717-2128.

3. H Schiff. "Mittheilungen aus dem Universitätslaboratorium in Pisa: Eine neue Reihe organischer Basen". *Annalen der Chemie und Pharmacie* 131.1 (1864): 118-119.

4. I Beloso., et al. "Flexidentate Behaviour of 2-Pyridylsulfonamides – Direct Electrochemical Synthesis and Spectroscopic and X-ray Characterisation of Neutral Copper (II) Complexes of *N* - (2-Pyridyl)sulfonamides". *European Journal of Inorganic Chemistry* 3 (2004): 635-645.

5. Chemistry, The Madura College, / Madurai Kamaraj University, India, Dr. A. Xavier, and N. Srividhya. "Synthesis and Study of Schiff base Ligands". *IOSR Journal of Applied Chemistry* 7.11 (2014): 06-15.

6. C Ainsworth. "Principles of modern heterocyclic chemistry (Paquette, Leo A.)". *Journal of Chemical Education* 46.9 (1969): 624.

7. P Selvam., et al. "Synthesis and anti-HIV activity of 4- (1,2-dihydro-2-oxo-3H-indol-3-ylidene) amino.-N (4,6-dimethyl-2-pyrimidinyl)-benzene sulfonamide and its derivatives". *European Journal of Pharmaceutical Sciences* 14.4 (2001): 313-316.

8. R B Singh., et al. "Analytical applications of thiosemicarbazones and semicarbazones: A review". *Talanta* 25.11-12 (1978): 619-632.

9. U Kulandaivelu., et al. "Synthesis, Antimicrobial and Anticancer Activity of New Thiosemicarbazone Derivatives". *Arch. Pharm. (Weinheim)* 344.2 (2011): 84-90.

10. W Hernández., et al. "Synthesis, Characterization, and In Vitro Cytotoxic Activities of Benzaldehyde Thiosemicarbazone Derivatives and Their Palladium (II) and Platinum (II) Complexes against Various Human Tumor Cell Lines". *Bioinorganic Chemistry and Applications* (2008): 1-9.

11. B Prathima., et al. "Copper (II) and nickel (II) complexes of benzyloxybenzaldehyde-4-phenyl-3-thiosemicarbazone: Synthesis, characterization and biological activity". *Spectrochimica Acta, Part A: Molecular and Biomolecular Spectroscopy* 77.1 (2010): 248-252.

12. P Kalaivani., et al. "Influence of terminal substitution on structural, DNA, Protein binding, anticancer and antibacterial activities of palladium (ii) complexes containing 3-methoxy salicylaldehyde-4 (N) substituted thiosemicarbazones". *Dalton Transaction* 41.8 (2012): 2486.

13. A J Kesel. "Broad-spectrum antiviral activity including human immunodeficiency and hepatitis C viruses mediated by a novel retinoid thiosemicarbazone derivative". *European Journal of Medicinal Chemistry* 46.5 (2011): 1656-1664.

14. EF Castro., et al. "Inhibition of Bovine Viral Diarrhea Virus RNA Synthesis by Thiosemicarbazone Derived from 5,6-Dimethoxy-1-Indanone". *Journal of Virology* 85.11 (2011): 5436-5445.

15. D L Klayman., et al. "2-Acetylpyridine thiosemicarbazones. 1. A new class of potential antimalarial agents". *Journal of Medicinal Chemistry* 22.7 (1979): 855-862.

16. G L Parrilha., et al. "Pyridine-derived thiosemicarbazones and their tin (IV) complexes with antifungal activity against Candida spp.". *European Journal of Medicinal Chemistry* 46.5 (2011): 1473-1482.

17. T S Lobana., et al. "Bonding and structure trends of thiosemicarbazone derivatives of metals—An overview". *Coordination Chemistry Reviews* 253.7-8 (2009): 977-1055.

18. D E Barber., et al. "Silane alcoholysis by a nickel (II) complex in a N, O, S ligand environment". *Inorganic Chemistry* 31.22 (1992): 4709-4711.

19. R P John., et al. "New copper (II) complexes of 2-hydroxyacetophenone N (4)-substituted thiosemicarbazones and polypyridyl co-ligands: structural, electrochemical and antimicrobial studies". *Polyhedron* 23.16 (2004): 2549-2559.

20. M A Ali., et al. "Four- and five-coordinate copper (II) complexes containing mixed ligands". *Polyhedron* 3.5 (1984): 595-598.

21. P Bindu., et al. "Epr, cyclic voltammetric and biological activities of copper (II) complexes of salicylaldehyde N (4)-substituted thiosemicarbazone and heterocyclic bases". *Polyhedron* 18.3-4 (1998): 321-331.

22. Z Lu., et al. "Deprotonated thioamides as thiolate S-donor ligands with a high tendency to avoid M-S-M bridge formation: crystal and molecular structure of bis (2-hydroxy-5-methylacetophenone N,N-dimethylthiosemicarbazonato)dinickel". *Inorganic Chemistry* 32.19 (1993): 3991-3994.

23. S Samanta., et al. "Utilization of LVO−2 species (L2− is a tridentate ONS donor) as an inorganic analogue of carboxylate group: A journey to a new domain of coordination chemistry". *Journal of Chemical Sciences* 118.6 (2006): 475-486.

24. S Padhyé and G B Kauffman. "Transition metal complexes of semicarbazones and thiosemicarbazones". *Coordination Chemistry Reviews* 63 (1985): 127-160.

25. A E Liberta and D X West. "Antifungal and antitumor activity of heterocyclic thiosemicarbazones and their metal complexes: current status". *Biometals* 5.2 (1992): 121-126.

26. E Lukevics., et al. "Neurotropic activity of aldehyde and ketone thiosemicarbazones with a heterocyclic component". *European Journal of Medicinal Chemistry* 30.12 (1995): 983-988.

27. R W Chesnut., et al. "Antibacterial activity of 15-azasteroids alone and in combination with antibiotics". *Steroids* 27.4 (1976): 525-541.

28. G Y Nagesh and B H M Mruthyunjayaswamy. "Synthesis, characterization and biological relevance of some metal (II) complexes with oxygen, nitrogen and oxygen (ONO) donor Schiff base ligand derived from thiazole and 2-hydroxy-1-naphthaldehyde". *Journal of Molecular Structure* 1085 (2015): 198-206.

29. I C Mendes., et al. "Coordination to copper (II) strongly enhances the in vitro antimicrobial activity of pyridine-derived N (4)-tolyl thiosemicarbazones". *Polyhedron* 26.13 (2007): 3263-3270.

30. M Salehi., et al. "Structural, spectroscopic, electrochemical and antibacterial studies of some new nickel (II) Schiff base complexes". *Inorganica Chimica Acta* 443 (2016): 28-35.

31. D X West., et al. "Nickel (II) complexes of 2-aminoacetophenone N (4)-substituted thiosemicarbazones". *Transition Metal Chemistry* (1998): 5.

32. R K Agarwal., et al. "Synthesis, Spectral, and Biological Properties of Copper (II) Complexes of Thiosemicarbazones of Schiff Bases Derived from 4-Aminoantipyrine and Aromatic Aldehydes". *Bioinorganic Chemistry and Applications* (2006): 1-10.

33. A P Rebolledo., et al. "Tin (IV) complexes of 2-benzoylpyridine *N* (4)-phenyl-thiosemicarbazone: spectral characterization, structural studies and antifungal activity: Tin (IV) complexes of 2-benzoylpyridine *N* (4)-phenylthiosemicarbazone". *Applied Organometallic Chemistry* 17.12 (2003): 945-951.

34. T N Sorrell., et al. "Synthesis and characterization of phenolate-bridge copper dimers with a copper-copper separation of >3.5 .ANG.. Models for the active site of oxidized hemocyanin derivatives". *Journal of the American Chemical Society* 107.14 (1985): 4199-4206.

35. M F Iskander., et al. "Synthesis, characterization and magnetochemical studies of dicopper (II) complexes derived from bis (*N*- salicylidene)dicarboxylic acid dihydrazides". *Journal of Coordination Chemistry* 58.2 (2005): 125-139.

36. S M Nasman. "N 2 S 2 -Donor Macrocycles with Some Transition Metal Ions: Synthesis and Characterization". *Phosphorus, Sulfur, and Silicon and the Related Elements* 183.7 (2008): 1541-1551.

37. B Bosnich. "An interpretation of the circular dichroism and electronic spectra of salicylaldimine complexes of square-coplanar diamagnetic nickel (II)". *Journal of the American Chemical Society* 90.3 (1968): 627-632.