Synthesis, structural characterization and biological activity of Cu(II), Co(II) and Ni(II) complexes derived from 2-(thiazol-2-ylimino)thiazolidin-4-one ligand

Ramona Khadivi, HodaPasdar*, NaserForoughifar, MehranDavallo

Department of Chemistry, Tehran North Branch, Islamic Azad University, Tehran, Iran.

Abstract—A novel series of metal complexes of 2-(thiazol-2-ylimino) thiazolidin-4-one ligand were prepared; the corresponding ligand was synthesized from reaction 2-Chloro-N-(thiazol-2-yl) acetamide with ammonium thiocyanate. The complexes are characterized by FTIR, UV-Vis, molar conductance and mass spectroscopy. The low molar conductance values indicate that the complexes are non-electrolytes. Spectroscopic studies confirmed that the ligand bonded to the metals through the sulphur atoms. Coordination number of copper and nickel complexes is four with square planar geometry, while the cobalt complex has octahedral geometry. In vitro antibacterial activity of ligand and its metal complexes was evaluated using well diffusion method and compared to the standard drug (tetracycline). The antibacterial activity was examined against Escherichia coli, and pseudomonas aeruginosa, as gram negative bacteria and Staphylococcus aureus as gram positive bacteria. It was found that Nickel complex has the highest antibacterial activity among the synthesized compounds with Zone inhibition diameter in the range 25-29 mm.

Keywords—thiazol, thiazolidine, sulphur atom, square planar, octahedral, antibacterial activity.

I. INTRODUCTION

Antimicrobial drugs are used to treat infection diseases caused by various pathogenic strains are essential medicines for human and animal health [1]. The treatment of infection is an important and requirement task [2]. Although there are already numerous classes of antibacterial agents, there has been some significant emerging resistance in most pathogenic bacteria to these drugs [3, 4]. For inhibition of this serious medical issue, it is essential to develop some new antibacterial agents or to expand the bioactivity of the previously used drugs. Metal-based antibacterial compounds appear to be a promising research to designing a novel therapeutic methodology for new antibiotic drugs to control and prevent the growth of bacterial strains [5].

In continuation of our previous studies in developing new antibacterial agents against resistant microorganisms, in the present work we report the synthesis of metal complexes derived from 2-(thiazol-2-ylimino)thiazolidin-4-one ligand [6]. This bioactive ligand has thiazole and thiazolidin moiety (Figure 1(a)). Recently, synthesis of thiazole and thiazolidin derivatives has shown much interest [7]. Thiazole ring as a common structural feature has been employed in various pharmacologically molecules and among the organic compounds, thiazolidin ligands have been investigated significantly [8]. Thiazolidin derivatives have variety of biological and industrial activities. The presence of a thiazolidine ring in penicillin was the first recognition of its presence in this drug. Thiazolidin-4-one represents a prevalent scaffold in drug discovery. Previous works showed that thiazolidin exhibit anti tubercular, antimicrobial, antioxidat and antifungal activity [9]. It has been reported that the presence of aryliden moieties at different positions of the thiazolidin ring improves its biological activity. Various researches have shown the tendency of this ligand to form complexes with radionuclides for potential use in nuclear medicine [10]. This ligand can coordinate to metal ions through either the nitrogen or the sulphur of the rings.

In this paper some new metal complexes were synthesized from 2-(thiazol-2-ylimino)thiazolidin-4-one ligand and tested for their in vitro antibacterial activities against Gram positive and Gram negative bacteria.

Fig.1(a): Structure of 2-(thiazol-2-ylimino)thiazolidin-4-one ligand.
II. METHODS

All the chemicals and solvents bought from Sigma-Aldrich and Fluka Company and were used without further purification. UV-Vis absorption spectra were recorded on a Cary 100 spectrophotometer. 1H-NMR spectra of ligand were performed on Brucker 250 MHz spectrometer in DMSO-d6 using tetramethylsilane as internal standard. The FTIR spectra were recorded using a Shimadzu 300 spectrometer. Melting points of the compounds were obtained by an electro thermal melting point apparatus and were not corrected. The progress of the reactions was monitored by thin layer chromatography (TLC) with silica-gel precoated sheets using n-hexane/EtOAC 1/3 as eluent; UV light was used for detection.

**General procedure for synthesis of metal complexes**

2-(thiazol-2-ylimino)thiazolidin-4-one (L) was synthesized according to previous literature [11]. First, a solution of (0.1 mmol) metal(II) chloride in methanol (10 mL) was prepared and then the solution of L (0.2 mmol) in methanol (25 mL) was added to it. The resulting mixture was refluxed for 4.5 h at 45°C. Followed by allowing it to stir overnight to ensure the completion of reaction.

After, the resulting solid was obtained from the solution by filtration it was washed and recrystallized with ethanol and finally dried in vacuum desiccator overnight.

**Copper (II) complex: [CuL2]** Dark green solid; 83%; M.p. 185-187 °C; FT-IR(KBr, cm-1): 3114, 3087, 2965, 2824, 2073, 1715, 1639, 919, 757; 1H NMR (250 MHz, DMSO-d6): δppm 12.13 (s, 1H, N-H), 7.60-7.59 (d, 1H, Aromatic-H), 7.41-7.40 (d, 1H, Aromatic-H), 4.00 (s, 1H, Aliphatic-H); UV/Vis (DMSO): λmax [nm] = 250, 300 nm; Mass: [m/z]+ = 199.

**Cobalt (II) complex: [CoL2Cl2]** Purple solid; 75%; M.p. 215-217 °C; Molar conductivity (Ω-1 mol-1 cm2): 10; FT-IR(KBr, cm-1): 3382, 3092, 2167, 1707, 1539, 6198; UV/Vis (DMSO): λmax [nm] = 305, 500 nm; Mass: [m/z]+ = 462.

**Nickel (II) complex: [NiL2]** Green solid; 68%; M.p. 220-222 °C; Molar conductivity (Ω-1 mol-1 cm2): 12; FT-IR(KBr, cm-1): 3379, 2924, 2800, 2433, 1648, 1580, 519, 488; UV/Vis (DMSO): λmax [nm] = 600, 680 nm; Mass: [m/z]+ = 530.

**Antibacterial activities**

The ligand and all the synthesized complexes were tested for their in vitro antibacterial activities against two Gram-negative (*Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 27853)) and one Gram-positive (*Staphylococcus aureus* (ATCC 25923)) bacteria strains using agar well-diffusion method. The tests were performed by the methodology recommended in the procedures of the National Committee for Clinical Laboratory Standards (NCCLS) [12]. The entire microorganism was cultured onto Muller-Hinton agar (MHA) medium and incubated for 18-24 h at 37°C. The synthesized compounds were dissolved in DMSO (100 µg/ml). Suspensions of each bacteria strain were reached from their 24 h cultures to obtain approximately 1.5 × 106 CFU/ml (colony forming units) and controlled with 0.5 McFarland turbidity standard. In the agar well-diffusion test, an amount of 20 ml sterile Muller-Hinton Agar and 100 µl of suspension of each bacteria were transferred to sterile petri dishes and allowed to solidify. The wells were tunnelled in the culture plates using a sterile cork borer (8 mm in diameter) and 100 µl of sample solution was poured to separate wells. Standard antibiotic drug (Tetracycline) was also used as positive control. The plates were incubated for 18-24h at 37°C. After this period of time, results were determined by measuring inhibition zones formed around each well as millimetres (mm) diameter.

III. RESULTS AND DISCUSSION

2-(thiazol-2-ylimino)thiazolidin-4-one (L) was synthesized according to previous literature [11] and the method for its synthesis is illustrated in Scheme 1. In the first step, 2-Chloro-N-(thiazol-2-yl)acetamide (2) was prepared from 2-aminothiazole (1) which through heterocyclization process under reflux condition in the presence of ammonium thiocyanate the corresponding ligand was achieved. The resulting ligand consists of thiazole and thiazolidine rings which could coordinate to the metal ions through sulphur atoms. All the metal complexes were obtained in high yield and characterized with molar conductance, FTIR, UV-Vis and Mass spectroscopy analysis.

![Scheme 1. Preparation of ligand.](image-url)
Table 1: Physical properties of synthesized compounds.

| compounds | M.W. (g/mol) | Color     | Yield (%) | Molar conductance | M.P (°C) |
|-----------|--------------|-----------|-----------|-------------------|----------|
| L         | 199          | Light-yellow | 92        | -                 | 185-187  |
| CuL       | 462          | Dark green | 83        | 10                | 215-217  |
| CoL       | 527          | Purple     | 75        | 15                | 220-222  |
| NiL       | 474          | Green      | 68        | 12                | 228-230  |

Characterization of Ligand

In the \(^1\)H-NMR spectrum of L the two aromatic protons appear at 7.40 and 7.60 ppm as doublet peaks. The signals of NH proton observed at 12.13 ppm while the aliphatic protons are shown at 4.03 ppm as a singlet peak. The H-NMR spectrum of ligand is shown in Figure 1.

![Fig. 1: The \(^1\)H-NMR spectrum of ligand.](image)

The FTIR spectra of L showed a strong peak at 3114 cm\(^{-1}\) indicating the N-H group, as well as CNS band appeared at 2073 cm\(^{-1}\). The C-H (aromatic) and C-H (aliphatic) stretching bands are appearing at 2965 and 2824 cm\(^{-1}\), respectively. Also a strong peak appeared at 1715 cm\(^{-1}\) due to the C=O stretching frequency and the C=N group was observed at 1639 cm\(^{-1}\).

In the UV-Visible spectrum of L two intense bands were observed at 250 and 300 nm. The former can be assigned to \(\pi\rightarrow\pi^*\) transition of aromatic ring and the later is due to the \(n\rightarrow\pi^*\) of –C=N and C=O groups.

The mass spectrum of the corresponding ligand is in good agreement with the proposed structure. The molecular ion peak for this compound was observed at \(m/z = 199\), which is equal to the molecular weight of this ligand. The mass spectrum of ligand is shown in Figure 2.
Characterization of metal complexes

Percent yields of metal complexes were in the range 68-83%. Among these metal complexes the highest yield was achieved for CuL metal complex (83%) with molar conductance of $10 \Omega^{-1} \text{cm}^{2} \text{mol}^{-1}$. The proposed structure of the metal complexes is shown in Figure 3.

In the UV-Visible spectra of all the complexes slight shifts are observed in intra ligand transitions to the lower wavelength compared to the free ligand. The copper (II) complex shows bands at 25, 310 and 510 nm due to the $\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ and $^2 \Sigma_g \rightarrow ^2 \Sigma_g$ transitions. Cobalt (II) complex shows peaks at 600 and 680 nm, while Nickel (II) complex shows absorptions at 360 and 420 nm. The d-d transitions are related to $^4 \Sigma_g \rightarrow ^4 \Sigma_g(p)$ and $^4 \Sigma_g \rightarrow ^4 \Sigma_g$ in Co(II) and $^3 \Sigma_g \rightarrow ^3 \Sigma_g$ in Ni(II) complexes. According to these transition, for Cu(II) and Ni(II) square-planer geometry are proposed, but octahedral geometry is suggested for Co(II) complex[13-15].

The mass spectra of the complexes are in good agreement with the proposed structures. The molecular ion peaks for the Cu(II), Co(II) and Ni(II) complexes were witnessed at $m/z= 462, 530$ and $474$ respectively, are equal to their molecular mass. The other peaks in the mass spectrum were attributed to the fragmentation of the complex obtained from the rupture of different bonds inside the molecule.

**Antibacterial activity**

Antibacterial activity of the parent ligand, its metal complexes and standard antibiotic drug (Tetracycline) were carried out against bacteria like *Escherichia coli*, and *Pseudomonas aeruginosa*, which represented as gram negative bacteria and *Staphylococcus aureus*, which served as gram positive bacteria, using Muller Hinton agar medium by well method. The evaluation of antibacterial effect, represented by measuring the diameter of inhibition zone, is shown in Table 2. Among all of the metal complexes, the compound with Ni metal ion showed maximum antibacterial activities with the zone inhibition diameter from 25-29 mm. The antibacterial activities against *Staphylococcus aureus* increased in the order: NiL>CoL> L>CuL. The antibacterial activities against *Escherichia coli* increased in the order: NiL>CoL>
The Cu complex has no antibacterial activity against this strain. Also the antibacterial activities against pseudomonas aeruginosa increased in the order: NiL > CoL.

| bacteria              | compounds | Staphylococcus aureus | Escherichia coli | pseudomonas aeruginosa |
|-----------------------|-----------|-----------------------|------------------|------------------------|
| L                     | 18        | 20                    | -                | -                      |
| CuL                   | 10        | -                     | -                | -                      |
| CoL                   | 24        | 25                    | 24               | -                      |
| NiL                   | 28        | 29                    | 25               | -                      |
| DMSO                  | -         | -                     | -                | -                      |
| Tetracycline          | 22        | 12                    | -                | -                      |

In general, the antibacterial activity of metal complexes was better than the parent ligand except in Cu complex which has a low activity against all the microorganisms. This phenomenon can be explained based on Tweedy’s chelation theory [16-18]. The chelation reduces the polarity of metal ion to some extent due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal. The chelation increases the delocalization of p-electrons over the whole chelate ring and enhances the lipophilicity of the complexes which, in turn, increases the penetration of the complexes into lipid membranes, and results in blockage of metal sites in the enzymes of the microorganisms. In addition, metal complexes hinder the respiration process of the cell, block the synthesis of proteins and prevent further growth of the organism.

IV. CONCLUSION

The corresponding ligand, 2-(thiazol-2-ylmino) thiazolidin-4-one (L) was prepared from reaction between 2-Chloro-N-(thiazol-2-yI) acetamidewith ammonium thiocyanate in good yield. In the next step, The copper(II), cobalt(II) and nickel(II) complexes were prepared by reaction of corresponding ligands and metal salts in molar ratio 2:1 (L:M). The ligand and its metal complexes were characterized by several spectroscopic methods. The results confirmed that the Cu(II) and Ni(II) complexes have square planar geometry while the Co(II) complexes have octahedral geometry. All the synthesized compounds were screened for their in vitro antibacterial activity against Gram-positive and Gram-negative microorganisms. The NiL complex showed highest antibacterial activity compared to other compounds.

ACKNOWLEDGEMENT

We grateful to thank the Islamic Azad University, Tehran North Branch for financial support.

REFERENCES

[1] Pasca C, Margheita L, Dezminarean D, Bobis O, Bonta V, Chirila F, Matei L, Fit N. Medicinal plants based products tested on pathogens isolated from mastitis milk. Molecules 2017: 22: 1473.

[2] Afraid M, Foroughifard N, Pasdar H, Moghanian H. Facile green one-pot synthesis of novel thiazolo [3,2-a] pyrimidine derivatives using Fe3O3@L-arginine and their biological investigation as potent antimicrobial agents. Appl Organometal Chem 2016: 31. doi: 10.1002/aoc.3683

[3] Rios J, Recio M, C, Medicinal plants and antimicrobial activity. J. Ethnopharmacol 2005: 100: 80–84.

[4] Ribet D, Cossart P, Microb Infect 2015: 17(3): 173.

[5] Pasdar H, HedayatiSaghavaz B, Foroughifard N, Davaloo M. Synthesis, Characterization and Antibacterial Activity of Novel 1,3-Diethyl-1,3-bis(4-nitrophenyl)urea and Its Metal(II) Complexes. Molecules 2017: 22: 2125.

[6] Khadivi R, Pasdar H, Foroughifard N, Davallo M. Synthesis and structural characterization of metal complexes derived from substituted guanidine-pyridine as potential antibacterial agents. Bio Interface research in applied chemistry 2017: 7(6): 2238-2242.

[7] Turan-Zitouni G, Demirayak S, Ozdemir A, Kaplanclipk Z, A, Yildiz M, T. Eur. J. Med. Chem 2004: 39: 267.

[8] Geronikaki A, Dearden J, Filimonov D, Galaeva I, Garibova T, L, Gloriozova T, Krajeva V, Lagunin A, Macaev F, Z, Molodavkin G, Poroikov V, Pogrebnoi S, I, Shepeli F, Voronina T, A, Tsitlakidou M, Vlad L, J. Med. Chem 2004: 47: 2870.

[9] Geronikaki A, Babaev E, Dearden J, Dehaen W, Filimonov D, Galaeva I, Krajeva V, Lagunin A, Macaev F, Molodavkin G, Poroikov V, Pogrebnoi
S, Saloutin V, Stepanchikova A, Stingaci E, Tkach N, Vlad L, Voronina T. Bioorg. Med. Chem 2004: 12: 6559.

[10] Gomez J. D. C, Balcazar E, Hagenbach A, Noufele C. N, Abram U. Benzoylamido-substituted thiazoles and thiazolidines and their rhenium complexes. Polyhedron 2016: 117: 293-299.

[11] Vicini P, Gerontakaki A, Anastasia K, Incertia M, Zania F. Bioorganic & Medicinal Chemistry 2006: 14: 3859–3864

[12] Wang X, Xie X, Cai Y, Yang X, Li J, Li Y. Design, synthesis, and antibacterial evaluation of some new 2-phenyl-quinoline-4-carboxylic acid derivatives. Molecules 2016: 21: 340.

[13] Kumaravel G, Uthra P. P, Raman N. Appl. Organomet. Chem. 2017.

[14] Ahmedova A, Marinova P, Paradowska K, Marinov M, Mitewa M. J. Mol. Struct. 2008: 892: 13.

[15] Shupak S. I, Biling E, Clark R. J. H, Williams R, Gray H. B. J. Am. Chem. Soc. 1964: 86(21): 4594.

[16] El-Megharbel S. M, Adam A. M, Meghdad A. S, Refat M. S. Synthesis and molecular structure of moxifloxacin drug with metal ions as a model drug against some kinds of bacteria and fungi. Russ. J. Gen. Chem. 2015: 85: 2366–2371.

[17] Patel M. N, Pansuriya P. B, Parmar P. A, Gandhi D. S. Synthesis, characterization and thermal and biocidal aspects of drug-based metal complexes. Pharm. Chem. J. 2008: 42: 687–692.

[18] HedayatiSaghavaz B, Pasdar H, Foroughifar N. Novel dinuclear metal complexes of guanidine-pyridine hybrid ligand: synthesis, structural characterization and biological activity. Biointerface research in applied chemistry. 2016: 6(6): 1842-1846.