Pharmacological activities of Transition Metal Complexes of Sulfathiazole drug: A Review

Richa Singh[1], Bharti Jain[2], Archana Singh[1] and Suman Malik[1]

1. Department of Chemistry, Sadhu Vaswani Autonomous College, Sant Hirdaram Nagar (Bairagarh) Bhopal, M.P. India.

2. Department of Chemistry, Government M. L. B. Girls Autonomous College Bhopal, M.P. India.

richasingh4177@gmail.com, bhartikjain@yahoo.com, drsingharchana@rediffmail.com, drsumanmalik@gmail.com

Abstract

In medicinal chemistry, the synthesis of sulfur-based compounds—more especially, sulfonyl or sulphonamide—is a rapidly developing field of study. The pharmacological characteristics of Sulfa drugs, mainly Sulfathiazole, have been widely described. Sulfathiazole is responsible for the formation of metals and their complexes. A significant role for transition metals in medical biochemistry. The property of most transition metals to form coordination complexes with neutral or anionic ligands. They exhibit multiple oxidation states which makes them suitable for use in drugs. This article reviews the various therapeutic applications of transition metal complexes of sulfonamide-based compounds.

Keywords – *Schiff bases, Transition metal complexes, Sulfa drugs, Sulfathiazole, Antimicrobial activity.*

1. Introduction

Sulfa drugs, also called sulphonamides (SO_2–NH-) [1], were the first effective antibacterial agents to be built in a pharmaceutical Laboratory [2]. It is also one among the first chemicals to be used consistently in the treatment and avoidance of bacterial infections in humans. Sulfa drugs are bacteriostatic. It means that they prevent bacteria from growing and multiplying but do not really destroy the organisms [3]. Organic compounds with a ring structure that contains sulphur, nitrogen, or oxygen as a heteroatom have been shown to be effective bioactive agents [4]. Sulfathiazole, a sulfa drug, is one of the family members of sulphonamides (sulfa drug) are used as a short-acting antibiotic. Formerly, it was a common oral and topical antimicrobial such as sulfathiazole ointment that was used in the treatment of pyogenic dermatoses [5] and is the most effective bioactive agent for bacterial infection prevention and treatment [6]. Sulfonamides were used as powerful chemotherapeutic agents for the prevention and treatment of bacterial infections in humans before antibiotics were developed and used to treat illnesses [7-8]. Sulfathiazole is still sporadically used, sometimes in combination with sulfabenzamide and sulfacetamide, and in aquariums [9]. It acts as a schiff base ligand which combines with the metals to form stable complexes. Schiff bases were first reported in 1864 by Hugo Schiff [10]. They play an important role in inorganic chemistry [11-12]. These are the substances that have an azomethine or imine group (-RC=N-). Typically, they are created when an active carbonyl and a primary amine condense [13-14]. Schiff bases are bi- or tri- dentate ligands which used in organic synthesis and medicinal chemistry to make carbon-nitrogen bonds with transition metals [15]. Schiff bases have very flexible and diverse structures [16.]

The elements with an incomplete d sub shell are known as transition metals; examples include Co (II), Mn (II), Fe (II), and Fe (III). Also, because of their unstable structural characteristics, these materials have changeable oxidation numbers and unstable electronic configurations that affect the biological system's variable redox system [17]. A significant role for transition metals in medical biochemistry [18]. The suitability of most transition metals for medicinal applications stems from their capacity to create coordination complexes with neutral or anionic ligands, as well as their ability to manifest various oxidation states. Metal complexes are well known for accelerating the effects of drugs. The coordination of a medicinal substance with a metal ion can frequently increase its effectiveness because the complexation of the metal ion and ligand may have synergistic effects.

The link and significance of metal-drug interactions have been shown by thorough study of the complex formation between metal ions and sulfa medications [19-22].

The challenge for researchers in this field is to design antimicrobial agents that have minimal side effects and high potency at the same time; taking into account the increasing resistance of microbes [23-24].

2. Pharmacological Activities of transition Metal Complexes

In this review paper, the therapeutic properties mainly antimicrobial activities of certain metal – Sulfathiazole complexes are described.

2.1 Antimicrobial Activity

Ifeanyi. E. Otuokere *et al.* documented the synthesis of a new Schiff base and its Ni(II) complex, making use of benzaldehyde and sulfathiazole. Elemental analysis, UV-visible spectra, FTIR, 1H-NMR, and 13C-NMR spectroscopy were used to describe them. In vitro tests were performed to determine the ligand's antibacterial sensitivity against E. coli, Pseudomonas aeruginosa, Staphylococcus aureus and Salmonella typhi. It was then discovered that the Ni(II) complex outperformed the Schiff base ligand in combating the bacterial strains. When compared to the Schiff base alone, the complex showed improved antibacterial activity [25].

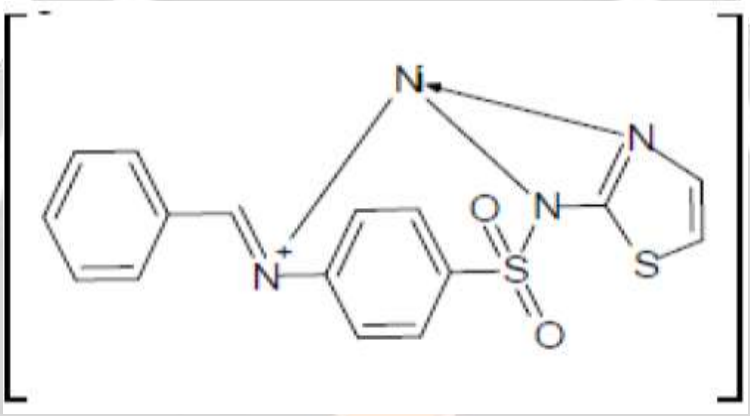

Fig:- Structure of Metal Complex.

Anacona *et al.* prepared metal coordination compounds using a cephalexin-based ligand obtained through the condensation of cephalexin antibiotics with sulfathiazole. The characterization of the material involved elemental and thermal analyses, molar conductance and magnetic susceptibility measurements, electronic spectra analysis, as well as FT-IR, EPR, and 1H NMR spectral studies. To evaluate the biological effects of the metal Schiff base complexes, both Gram-positive and Gram-negative bacteria were employed. The complexes exhibited a higher preference for biological activity compared to the unbound ligands [26].

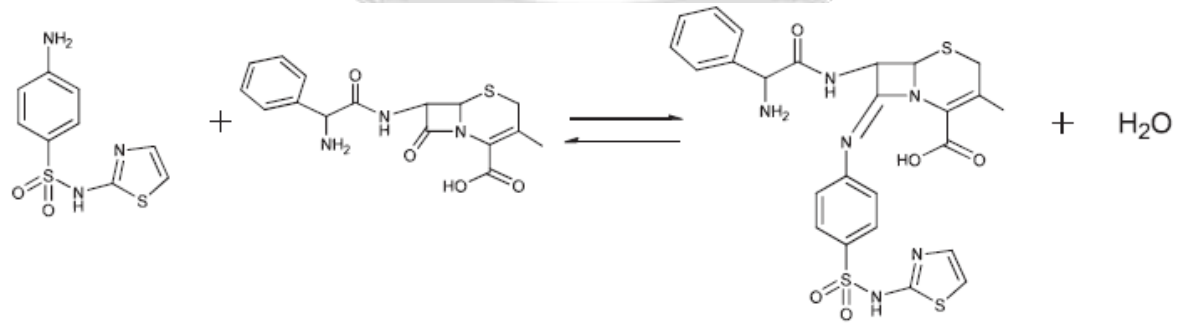

Fig:- Structure of Schiff base.

Samir T. Gaballah *et al.* synthesized a number of novel sulfathiazole compounds derived from N-(3-acetylthiazol-2(3H)-ylidene)-4- aminobenzenesulfonamide. 1H, 13C, 2D 1H Microanalyses, NMR, and MS all confirmed the generated compounds' structural integrity. Gram-positive and Gram-negative bacteria, along with fungal strains, were examined for the antimicrobial activity of the chemicals generated. The findings revealed that some of the chemicals under investigation had a particularly high potency [27].

Yoseph Samuel *et al.* have created One thiazole derivative and two novel sulfathiazole compounds have been created. Utilizing spectroscopic techniques 1H, 13C NMR and their melting points, the generated compounds were characterised. The antibacterial activity of the produced substances were tested in vitro against two Gram-positive and two Gram-negative bacteria, including *E. coli* and *P. aeruginosa (S. pyogenes* and *S. aureus)* respectively. Nutrient broth was used as the inoculation medium, and it was incubated at 37°C overnight. When compared to a typical medication, substance had an inhibition zone and had strong inhibitory action against Gram-negative E. coli [28].

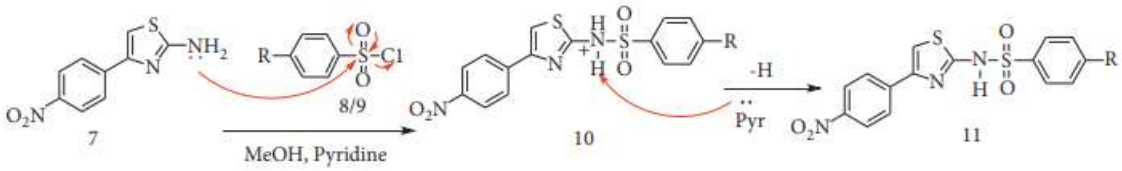

Fig:- Synthesis of the compound.

J. R. Anacona *et al.* focused on Nickel metal. To form [Ni(L)(stz)(H2O)x]n complex of cefazolin, cephalothin, cefotaxime, ceftriaxone and [Ni(L)(stz)(H2O)x]n, nickel(II) combines with cephalosporins and s (L5). The compounds are not soluble in water or other common organic solvents, even though the [Ni(L5)(stz)]Cl complex is a 1:1 electrolyte in DMSO. It is highly probable that polymeric structures are present. They were tested for antibacterial activity and the results were compared to commercial activityThe complexes' antibacterial properties outperformed those of Hstz and the initial metal salt [29].

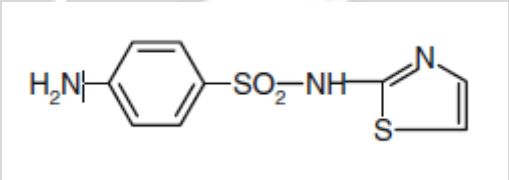

Fig:- Structure of the ligand.

Pontoriero, A., Mosconi synthesized a new Co(III)-sulfathiazole complex: Costz. FT-IR spectrometry, thermal analysis, UV-VIS spectroscopy, and 1H NMR have all been employed to investigate the structure of this substance. The deformed octahedral environment of the Co(III) ion might coordinate with the N thiazolic atom of sulfathiazolate. *In vitro* testing of the Costz complex for antimicrobial and antifungal activity against *Aspergillus fumigatus* and *Aspergillus flavus* revealed mild antifungal activity against *Aspergillus fumigatus* and *Aspergillus flavus*. In vitro, Costz complex showed increased antibacterial activity against *Pseudomonas aeruginosa* when compared to the ligand. In comparison to their parent ligand, mixed ligand Co (III) complexes had good antimicrobial activity [30].

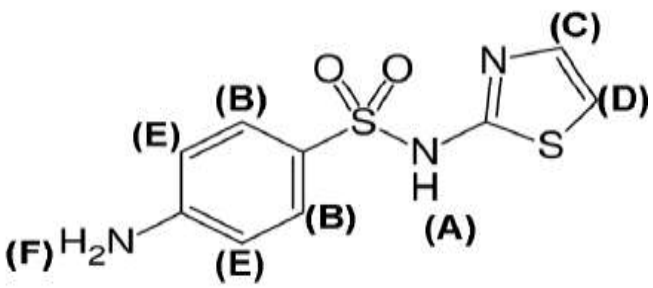

Fig:- Sulfathiazole (Hstz; as sodium salt: Nastz). Labels indicate the notation used for Hstz and their derivatives for 1H NMR assignments.

A. Reiss *et al.* synthesized Co(II), Ni(II), and Cu(II) complexes with the Schiff base ligand. It is made by condensing salicylaldehyde and sulfathiazole. Thermal analysis, spectroscopic methods, molar conductance, and elemental analysis were used to characterise them.obtained by the condensation of sulfathiazole with salicylaldehyde. Several bacterial strains (*Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus*, and *Bacillus subtilis*) were tested against the Schiff base and its metal complexes. The findings indicated that all the complexes have greater antibacterial activity than the Schiff base alone [31].

Rama and R. Selvameena formed metal chelates using Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) acetates with a Schiff base ligand derived from sulfathiazole and 5-nitro salicylaldehyde (HL). and 5-nitro salicylaldehyde (HL). The structural characterstics of both the ligands and their complexes were determined through various analytical techniques, including microanalytical data, electrical conductance, FT-IR, 1H and 13C NMR, UV-Visible spectra, magnetic moment studies, thermal analysis, EI-mass spectra, and powder XRD studies. Their antioxidant and antibacterial activities were also investigated. The ligand's antioxidant property is strong, as evidenced by a decrease in activity against the ABTS assay when complexed with metals [32].

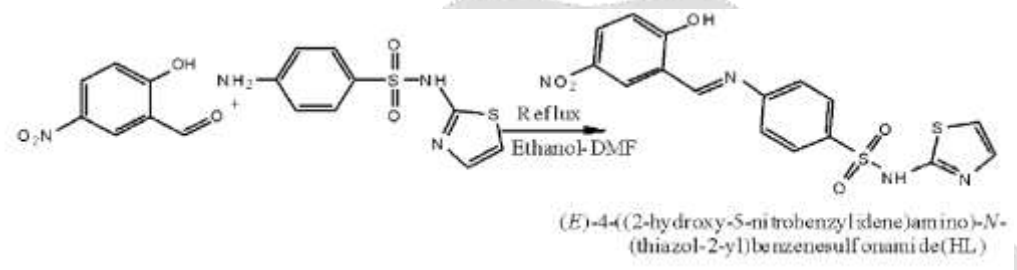

Fig:- Formation of ligand HL

Farah Ali Dawood *et al.* employed both chemical and electrochemical techniques to synthesize complexes of Co(II), Ni(II), Cu(II), and Mn(II) incorporating Schiff base NOS donor ligands. Measurements of conductance, magnetic susceptibility and elemental analysis have all been used to determine the complexes' structures. IR, thermal techniques (TGA and DTA). Gram positive *(Staphylococcus aureus and Bacillus subtilis)* and Gram negative bacteria have been tested for the Schiff base's antimicrobial properties *(Escherichia coli and Pseudomonas aeruginosa)*. On the above mentioned bacteria, most metal complexes inhibit bacteria far more than the Schiff base [33].

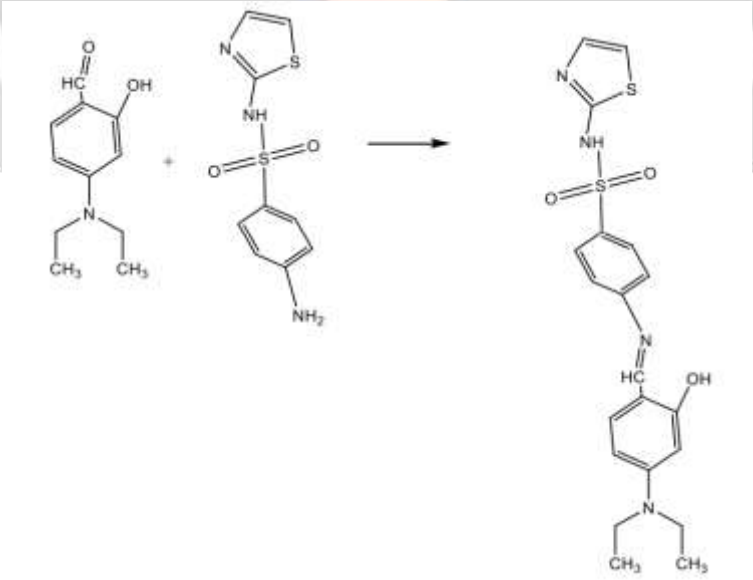

Fig:- Formation of ligand.

V. Gomathi and R. selvameena have described the synthesis of new Schiff bases derived from sulfathiazole with three different aldehydes: 3-ethoxysalicylaldehyde, pyridine-2-carbaldehyde, and 2-hydroxy-1-naphthaldehyde. The synthesized Schiff bases were screened for antibacterial activity against *Staphylococcus aureus* and gram-negative bacteria (*E.Coli*, *Klebsiella sp*, and *Pseudomonas aeruginosa*), as well as antifungal

activity against *Aspergillus niger* and *Mucor.* Analytical data, IR, 1H NMR, 13C NMR, UV-Vis spectra, and the disc diffusion method were employed for characterization. The Schiff bases exhibited remarkably potent antibacterial and antifungal effects against both Gram-positive and Gram-negative microbes, as evidenced by the observed zone of inhibition [34].

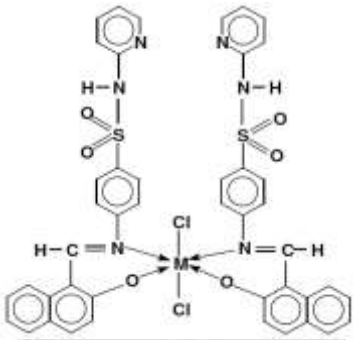

Fig:- Structure of complex.

Bellú, S., Hure, E *et al.* prepared the metal complexes (1) [CoII(ST)2(H2O)3]n (2) ((ST) = sulfathiazolate) [CoII(ST)2(H2O)4] by reacting sulfathiazole and cobalt(II). In both molecules, the Co(II) ion is in an octahedral environment. In the area of the IR bands that corresponds to amine group signals, differences between them were visible. [CoII(ST)2(H2O)4] was found to be effective against *Aspergillus fumigatus* (the same as the ligand) and *Aspergillus flavus* in tests to identify its antifungal properties (better than the ligand) [35].

M. Sivasankaran Nair created the compound of sulfathiazole (stz), a ligand, and mixed ligand systems with Cu(II). The complex was then characterised by TGA, DTA, ESR, UV, IR, X-Ray etc. The complexes' biological effects on yeast *(Saccharomyces cerevisae), bacteria (Salmonella typhi),* and *fungus* were evaluated *(Lapsiodiplodia theobrome* and *Fusarium oxysporum).* Complexes with mixed ligands have greater activity [36].

J. Casanova *et al.* synthesised and evaluated a compound of copper (II) having the formula Cu2(stz)4 (stz-) sulfathiazolato) using spectroscopic methods. The structure is made up of dinuclear copper(II) units with four sulfathiazolato ligands that form a nonlinear NCN group that connects the metal ions. The Schiff bases demonstrated remarkably strong antibacterial activity against both Gram-positive and Gram-negative microorganisms [37].

L. Figueroa *et al.* studied the biological activity of sulfathiazole complex. To assess the antibacterial efficacy of a sulfathiazole derivative against Staphylococcus aureus and Vibrio cholerae, cefotaxime, gentamicin, ciprofloxacin, and sulfathiazole were used as controls. The antibacterial activity of several chemicals on various bacterial species was assessed using the microbial minimal inhibitory technique. New aliphatic sulphonamides have been found to have better antibacterial activity against *Staphylococcus aureus* and other pathogens, according to reports [38].

I.E. Otuokere *et al.* were able to create Schiff base 4-{[(E)-Phenylmethylidene]amino}-N-(1,3-thiazol-2-yl)benzenesulfonamide (PTSA) by combining sulfathiazole with benzoyl acetone. Mn(II) complex of PTSA was prepared. Electronic spectra, FTIR, 1H NMR, and elemental analyses were used to characterise the compound. Biological activities were tested. The end result showed that the metal Schiff bases' antioxidative and antibacterial properties were improved more than the Schiff base itself [39].

Conclusion –

This review paper contains numerous research papers that are of great importance in the field. The formation of transition metal complexes with organic ligands has been made possible by recent advances in inorganic chemistry. Numerous metal complexes have antibacterial qualities that are effective against both Gram positive and Gram negative microorganisms, according to scientific research. Also, in vitro screening was conducted against bacteria and fungi to determine whether the Sulfathiazole-derived metal complexes have antimicrobial, antibacterial and antifungal properties. It is noted that metal complexes formed from sulfathiazole have much higher biological activity than their parent ligands.

Acknowledgement -

The authors acknowledge the Principal Sadhu Vaswani Autonomous College, Bairagarh, Bhopal, for providing necessary amenities for research work and DST for granting the FIST program to the college.

References -

1. C. Ordoñez, M. Reyes, C. Santibáñez, S. M. Hernández, B. García, G. Rivera, Efficient synthesis of sulfonamide derivatives on solid supports catalysed using solvent-free and microwave-assisted methods. *Quim. Nova*, 34.5 (2011), 787-791.
2. S. Jayachandran, A. L. Muney, and K. V. Smith, Modern Medicine and the Twentieth Century Decline in Mortality: Evidence on the Impact of Sulfa Drugs, *American Economic Journal,* 2.2 (2010), 118-146.
3. Sharma, Ram Naresh, Synthesis Characterization and biological studies of some transition Metal Complexes of New Schiff Bases of Sulfa Drugs. *PhD Thesis*, Jiwaji University, Gwalior, (2010).
4. S. Akral and V. Singh, "Recent development on importance of heterocyclic amides as potential bioactive molecules: A Review," *Current Bioactive Compounds*,15.3, (2019), 316–336.
5. J. R. Anacona and M. Lopez, Mixed-Ligand Nickel(II) Complexes Containing Sulfathiazole and Cephalosporin Antibiotics: Synthesis, Characterization, and Antibacterial Activity, *Hindawi, International Journal of Inorganic Chemistry* (2012).
6. Y. Samuel, A. Garg, and E. Mulugeta, Synthesis, DFT Analysis, and Evaluation of Antibacterial and Antioxidant Activities of Sulfathiazole Derivatives Combined with *In Silico* Molecular Docking and ADMET Predictions, *Hindawi , Biochemistry Research International, (* 2021), 14.
7. T. Kamimura, Y. Matsumoto, N. Okada, "Ceftizoxime (FK 749), a new parenteral cephalosporin: in vitro and in vivo antibacterial activities," *Antimicrobial Agents and Chemotherapy*, 16.5(1979), 540–548.
8. K. P. Fu and H. C. Neu, "Antibacterial activity of ceftizoxime,a *β*-lactamase-stable cephalosporin," *Antimicrobial Agents and Chemotherapy*,17.4 (1980) 583–590.
9. F.M. Gordin, G.L. Simon, C.B. Wofsy , *J*. Mills, Adverse reactions to trimethoprim-sulfamethoxazole in patients with the acquired immunodeficiency syndrome, *Ann. Intern. Med.,* 100.4, (1984), 495-499.
10. Schiff, H. (1864). Mittheilungen aus dem Universitätslaboratorium in Pisa: eine neue Reihe organischer Basen. *Justus Liebigs Annalen der Chemie*, *131*(1), 118-119.
11. A.W. Kleij, Nonsymmetrical salen ligands and their complexes: Synthesis and applications, Eur. J. Inorg. Chem., 193- 205, 2009.
12. P. Das, W. Linert, Schiff base-derived homogeneous and heterogeneous palladium catalysts for the Suzuki–Miyaura reaction, Coord. Chem. Rev., 311, 1-23, 2016
13. Arulmurugan, S., Kavitha, H. P., & Venkatraman, B. R. (2010). Biological activities of Schiff base and its complexes: a review. *Rasayan J Chem*, *3*(3), 385-410.
14. [6] Moffett, R.B. and Rabjohn, N. (1963). *Organic Synthesis*. *Vol*. *4*, *John Wiley* & *Sons*, *Inc*., *New York*, *605*.
15. Natta, G. (1955). P. Pino, P. Corradini. F. Danusso, E. Mantica. G. Mazzanti, and G. *Moraglio. J. Am. Chem. Sot*, *77*, 1708.
16. [C. Imrie, P. Kleyi, V. O. Nyamori, T. I. A. Gerber, D. C. Levendis, J. Look, J. Organomet. Chem., (2007), pp 692-3443].
17. A. Bagchi, P. Mukherjee, A. Raha, A Review on Transition Metal Complex – Modern Weapon in Medicine. *International Journal of Recent Advances in Pharmaceutical Research 5*.3(2015), 171-180.
18. S. Rafique, M. Idrees, A. Nasim, H. Akbar, & A. Athar , Transition metal complexes as potential therapeutic agents. *Biotechnology and Molecular Biology Reviews*, *5*.2(2010), 38-45
19. J. Casanova, G. Alzuet, S. Ferrer, J. Borras, S. Garcia-Granda, and E. Perez-Carreno, "Metal complexes of sulphanilamide derivatives. Crystal structure of [Zn(sulfathiazole)2] · H2O," *Journal of Inorganic Biochemistry*, 51.4(1993), 689–699.

20. J. Casanova, G. Alzuet, J. Borras, J. Latorre, M. Sanau, and S. Garcia-Granda, "Coordination behavior of sulfathiazole. Crystal structure of [Cu (sulfathiazole)(py)3Cl] superoxide dismutase activity," *Journal of Inorganic Biochemistry*, 60.3(1995), 219–230.

21. J. Casanova, G. Alzuet, J. Borras, J. Timoneda, S. Garcia- Granda, and I. Candano- Gonzalez, "Coordination behaviour of sulfathiazole. Crystal structure of dichloro- disulfathiazole ethanol Cu(II) complex. Superoxide dismutase activity," *Journal of Inorganic Biochemistry*, 56.2(1994), 65–76.
22. J. Casanova, G. Alzuet, J. Borr´as, and O. Carugo, "Crystal structures and superoxide dismutase mimetic activity of [CuL2(Him)2]·MeOH and [CuL2(mim)2]·H2O [HL = 4- amino-N-(thiazol-2-yl)benzenesulfonamide, Him = imidazole, mim = N-methylimidazole]," *Journal of the Chemical Society-Dalton Transactions*, 11(1996), 2239–2244.
23. D. Lin , M.J. Tucker, M.J. Rieder, Increased adverse drug reactions to antimicrobials and anticonvulsants in patients with HIV infection, *Ann. Pharmacother.*, 40.9 (2006), 1594-1601.
24. M. Summan, A.E. Cribb, Novel non-labile covalent binding of sulfamethoxazole reactive metabolites to cultured human lymphoid cells,*Chem.-Biol. Interact.*, 142.1.2, (2002),155-173.
25. Otuokere, E. Ifeanyi, J. C. Anyanwu, and K. K. Igwe. Ni (II) Complex of a Novel Schiff Base Derived from Benzaldehyde and Sulphathiazole: Synthesis, Characterization and Antibacterial Studies, *Communication in Physical Sciences*, 5.1, 2, 3 (2010).

26. JR Anacona, R Salazar, J Santaella, F. Celis, Synthesis and characterization of transition metal complexes with a Schiff base derived from cephalexin and 1, 2–diaminobenzene. antibacterial activity, *Inorganic and Nano-Metal Chemistry* 48.8 (2018), 404-411.

27. S.T. Gaballah, H. Amer, A. Horvath, Al-Moghazy, M. and M.I. Hemida, Synthesis, antimicrobial, and docking investigations of remarkably modified sulfathiazole derivatives. *Egyptian Journal of Chemistry*, *63*.1(2020), 71-184.

28. Y Samuel, A Garg, E Mulugeta, Synthesis, DFT Analysis, and Evaluation of Antibacterial and Antioxidant Activities of Sulfathiazole Derivatives Combined with In Silico Molecular Docking and ADMET Predictions. *Biochemistry Research International*, 2021.

29. J. R. Anacona, and O. Ivor, Synthesis and antibacterial activity of copper (II) complexes with sulphathiazole and cephalosporin ligands, *Transition Metal Chemistry* 33.4 (2008), 517-521.

30. A Pontoriero, N Mosconi, L Monti, S. Bellu, AM Williams, N. Bibiana, and R. Marcela, Synthesis, characterization and biological studies of a cobalt (III) complex of sulfathiazole, *Chemico-Biological Interactions* 278(2017), 152-161.

31. A. Reiss, N. Cioateră, A. Dobrițescu, M. Rotaru, A.C. Carabet, F. Parisi, A. Gănescu,I. Dăbuleanu, C.I. Spînu, and P. Rotaru, Bioactive Co (II), Ni (II), and Cu (II) complexes containing a tridentate sulfathiazole-based (ONN) Schiff base. *Molecules*, *26*.10 (2021), 3062.

32. I Rama and R. Selvameena, Manganese (II), cobalt (II), nickel (II), copper (II) and zinc (II) complexes of sulfathiazole functionalised Schiff base: Synthesis, characterization, redox behavior, antioxidant and antimicrobial activities. *J. Indian Chem. Soc*, *97*.11a(2020), 2144-2154.

33. Dawood, F. Ali, F. L. Yahya, and R. K. Raheem Al-shemary, Preparation and Characterization of sulfathiazole Schiff Base Complexes of Co (II), Ni (II), Cu (II), and Mn (II), *NVEO-NATURAL VOLATILES & ESSENTIAL OILS Journal| NVEO* (2021), 8991-9003.

34. V. Gomathi and R. Selvamena, Synthesis, Characterization and Biological Activity of Schiff Base Complexes of Sulfa Drug with Transition Metals, *Asian Journal of Chemistry*, 2012.

35. S. Bellú, M. Rizzotto, N. Okulik, and A. Jubert, The interaction between sulfathiazole and cobalt (II): potentiometric studies. *Química Nova*, *30*.5(2007), 136-1142.

36. M.S. Nair and S. Regupathy, Studies on Cu (II)-mixed ligand complexes containing a sulfa drug and some enzyme constituents, *Journal of Coordination Chemistry, 63.2 (2010) 361-372.*

37. J. Casanova, G. Almet, §. Ferrer, J. Borrk, S. Garcia-Grmda, and IE. Perez-Carrefio, .). Metal complexes of sulfanilamide derivatives. Crystal structure of [Zn (sulfathiazole) 2]· H2O. Journal of inorganic biochemistry, 51.4(1993), 689-699.

38. L. V. Figueroa, D.C. Francisco, E. C. García, E. G. Pool, M. N. Rosas, and M. R. López. Design and synthesis of two sulfathiazole derivatives using a three-component system, *Bulgarian Chemical Communications* (2013), 332.

39. I.E. Otuokere, J. C. Anyanwu, and K. K. Igwe, Synthesis, Spectra and Antibacterial Studies of 4-{[(E)-phenylmethyl-idene] amino}-N-(1, 3-thiazol-2-yl) benzenesulfonamide Schiff Base Ligand and its Ni (II) Complex, *Communication in Physical Sciences* 7.2(2021).