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Review Article

Schiff base complexes derived from Trimethoprim

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ABSTRACT

Trimethoprim (TMP) is currently frequently utilized in modern medicine due to its organic features. Trimethoprim inhibits vulnerable organisms from converting dihydrofolate to tetrahydrofolate, which is the active form of folic acid. Its heterocyclic substances are crucial to the fields of medicine and pharmacology by reacting to their Schiff base derivatives with metals. The preparation and detailed analysis of these compounds were conducted using diverse physicochemical techniques, including measurements of electronic conductivity, UV-visible spectral analysis,1H-NMR, 13C-NMR spectroscopic studies, atomic absorption evaluations and CHN elemental composition determination. The antimicrobial activity of TMP-based compounds was demonstrated by their ability to suppress the development of pathogenic microorganisms, including Gram-positive (G+) strains such as Staphylococcus pyogenes and Bacillus subtilis, alongside Gram-negative strains like Shigella flexneri.

Keywords: Trimethoprim, Schiff bases, metal complexes, biological activity

Introduction

In chemistry, a major revolution was caused by compounds containing nitrogen, sulfur, or oxygen atoms, especially TMP, due to its effectiveness in many areas of medicine, including its effectiveness as antiparasitic, antibacterial, anticancer, antimalarial, antitumor, and antiviral agents [1]. Roth and colleagues described TMP for the first time as a broad-spectrum antimicrobial agent with antiparasitic activity (Figure 1) [2].

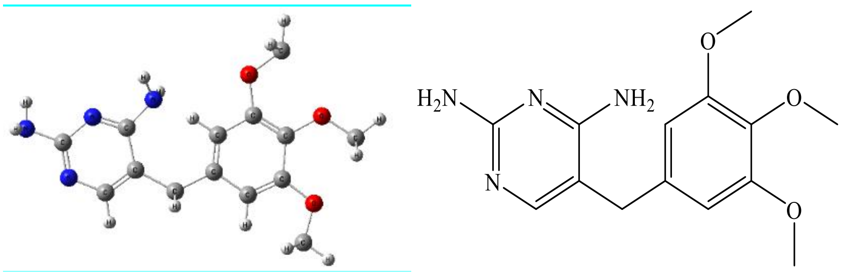
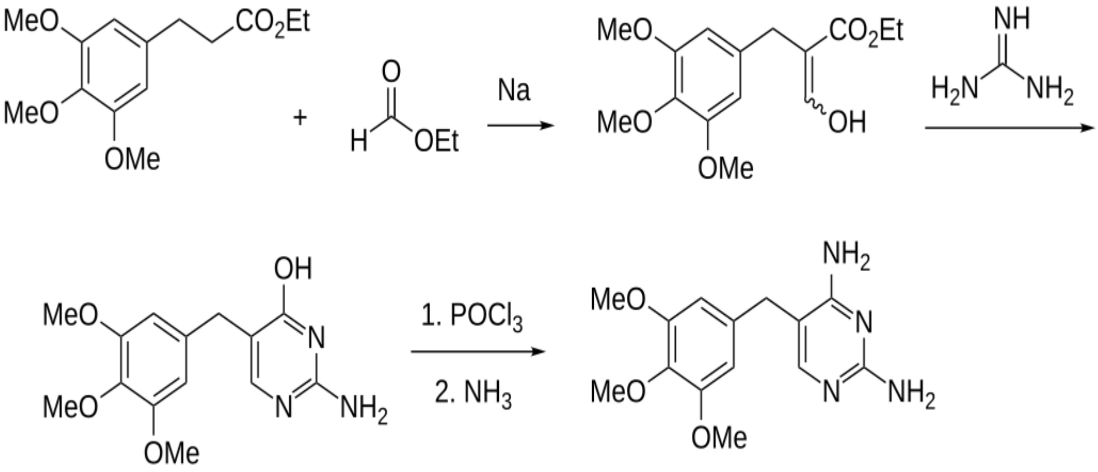


Figure 1. Configuration and 3D -geometrical configuration of the TMP [3]

TMP, also identified as $5-(3{,}4{,}5-trimethoxybenzyl)-2{,}4-diaminopyridine$, is a broad-spectrum antibacterial agent treatment that is applied to treat infections of the urinary tract, and preventative measures [4]. The following scheme illustrates how it competitively inhibits dihydrofolate reductase as a structural equivalent of the pteridine component of dihydrofolic acid [5].



Scheme 1. Preparing rote of TMP [5].

Because of their amide structure, TMP is categorized as a heterocyclic molecule. The production of new compounds combining TMP amides and derivatives of maleimide uses amide as a starting material [6]. Heterocyclic compounds are the primary line of treatment for inflammatory conditions such as arthritis [7]. Gram-positive (G^{+}) and Gram-negative (G^{-}) bacteria, as well as a variety of fungi, are susceptible to trimethoprim's potent antibacterial and antifungal activities [8]. Metal-drug complexes have generated a great interest and resulted in several novel and practical drugs. Research is still being conducted in several disciplines [9–20].

One notable and significant hydrocarbon derivative in organic synthesis that includes the Azomethine group $(C=N)$ as a functional group is a Schiff base. It can be produced by a straightforward reaction of condensation between aldehydes or ketones and main amines. The imine compounds a**re employed as ligands, using the azomethine nitrogen atom to coordinate with metal ions**. metal ions. Depending on the position and number of electron-donating groups, Schiff base derivatives complexed with various metal ions demonstrated the ability to create unimetallic, bimetallic or polymetallic species, which in turn function as ligands with one, two or three donor atoms in coordination bonds [21].

A Schiff base prepared from TMP involves the formation of an imine (Schiff base) by reacting the primary amine group in TMP with a carbonyl compound, such as an aldehyde or ketone. TMP, an antibacterial drug, contains amino groups that are capable of participating in Schiff base formation [22].

The importance and applications of Schiff bases derived from TMP

Schiff bases derived from TMP have attracted considerable attention for their diverse pharmaceutical applications. Modifying TMP to form Schiff bases have been shown to enhance its antimicrobial, antifungal, and antiparasitic activities. These structural modifications may improve therapeutic efficacy, particularly against resistant bacterial strains, by altering the drug's interaction with key bacterial enzymes such as dihydrofolate reductase. In addition, TMP–Schiff base complexes with transition metals such as Cu(II), Zn(II), and Co(II) are being investigated for their ability to further increase antimicrobial and antifungal potency. The incorporation of metal ions can influence metal–ligand interactions, potentially introducing new mechanisms of action that strengthen biological activity. Schiff bases derived from TMP also hold promise in drug delivery systems, where they may be used to modify solubility, stability, or release characteristics, resulting in formulations with enhanced pharmacokinetic properties. Beyond pharmaceutical applications, TMP-based Schiff bases have relevance in environmental and analytical chemistry, particularly for detecting and chelating metal ions in environmental or biological samples. Their strong metal-binding capabilities make them useful in environmental remediation, including the removal of heavy metals from contaminated water sources. Overall, Schiff bases prepared from TMP represent versatile compounds with significant potential for improving antibacterial performance, developing metal-based therapeutic agents, and contributing to environmental applications.

Coordination complexes of Schiff bases origination from TMP

The proposed structure of the metal complexes, TMP with p-Chlorobenzalehyde (pb) and TMP with Vanillin (V), coordinated with$Ni(II)$, $Zn(II)$, $Mn(II)$, and $Co(II)$ at pH between 7-8, has been confirmed by Joshi and Pawar's analysis. The Schiff base ligands have been demonstrated to have proved biologically active, and their metal complexes exhibit enhanced antimicrobial activity against one or more strains. The chelation process tends to make the ligands act as more effective and influential bactericidal agents (Figure 2)[25]. For each complex, an octahedral form was suggested.

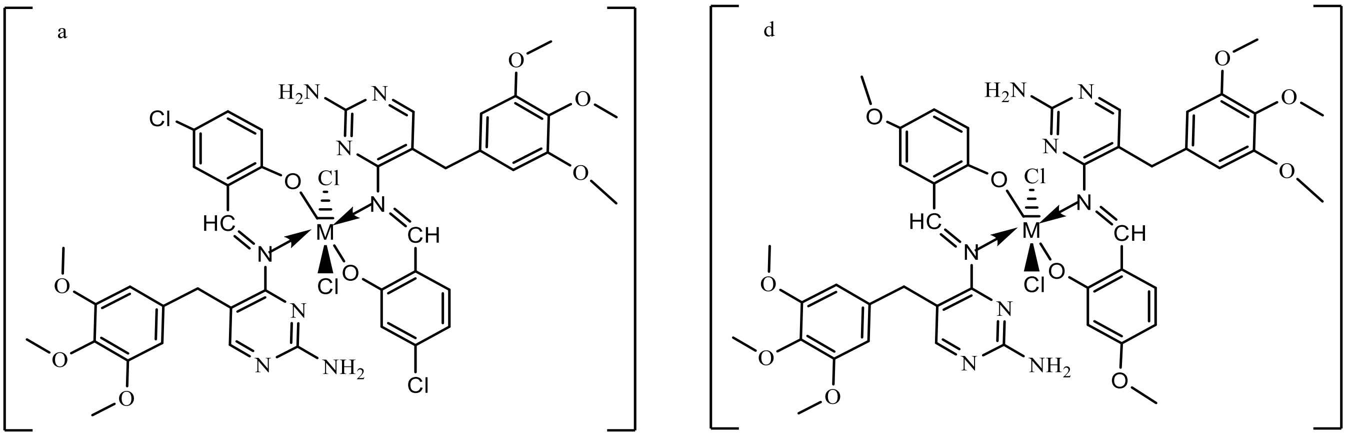
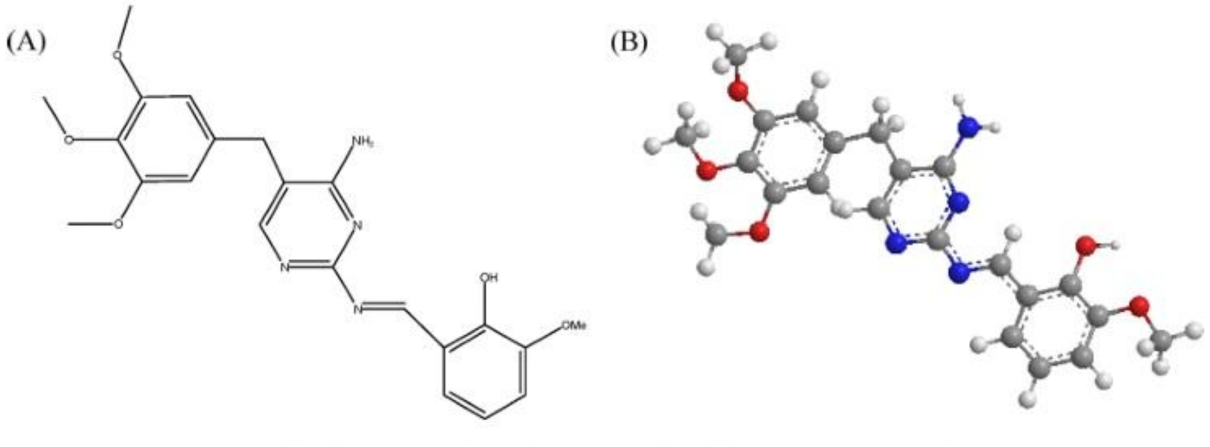


Figure 2. (a): Metal complex PbTM, (b): Metal complex VTM.

Lia and his associates used equal amounts of TMP and o-vanillin to create Valen Shiff base ($C_{22}H_{24}N_4O_5$). It has been studied how the Schiff base interacts with bovine serum albumin (BSA) . It was confirmed a big development of a Schiff base-BSA complex is what causes the inhibition of fluorescence of BSA caused using Schiff base. At various thermal state, the system's thermodynamic values G, H, and S were computed. Additionally, the distance r from the acceptor (Schiff base) and donor (Trp. 213) was measured. According to simultaneous fluorescence spectroscopy findings, BSA's molecular conformation was altered by the connection with Shiff base (Figure 3) [26].



(a) (b)

Figure 3. Molecular framework (a) and 3D conformation (b) of the synthetic Valen Schiff base.

Numan and his team utilized microwave irradiation to synthesize a new Schiff base ligand [HL] by reacting TMP with 2-benzoyl benzoic acid. The ligand [HL] was combined with 8-hydroxyquinoline [HQ] and various metal salts, including: $M = Mn(II), Co(II),\ Ni(II),$ $Cu(II), Zn(II)$, and $Cd(II)$ in ethanol using a $1:1:1$ molecular ratio, this process yielded six-coordinated metal ligand complexes with an octahedral shape which demonstrated significant antibacterial activity opposed to various bacterial strains, as depicted in (Figure4) [27].

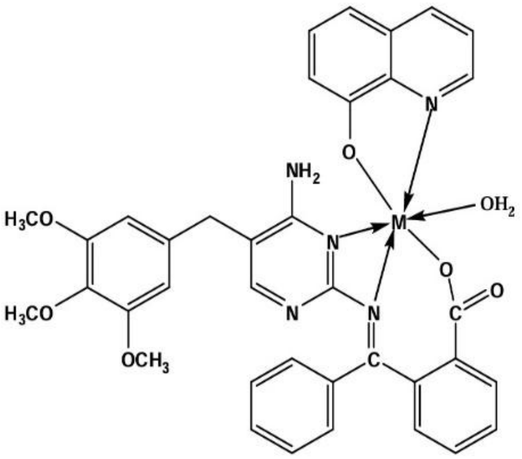
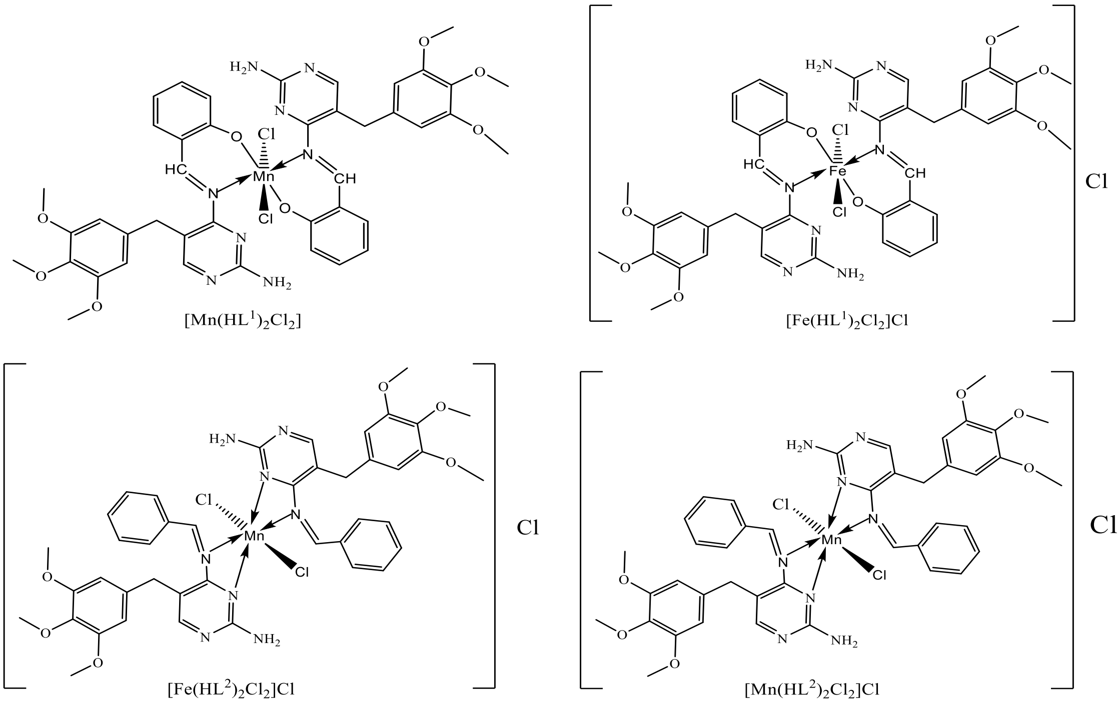


Figure 4. The proposed structure for mixed ligand complexes.

Ndahi and his team created and studied the complexes of $Mn(II)$ and $Fe(III)$ using HL^1 in addition HL^2 TMP Schiff base as ligands, which are made from 2-hydroxybenzaldehyde and phenylmethanal, respectively. The spectroscopic results show that strong coordination bonds are being formed between the ligands and metal centers. Antibacterial evaluations showed that Fe(III) complexes were more effective at killing bacteria than Mn(II) complexes; they were even better than the usual drug TMP (Figure 5) [28].


$[Mn(HL^1)_2Cl_2]$

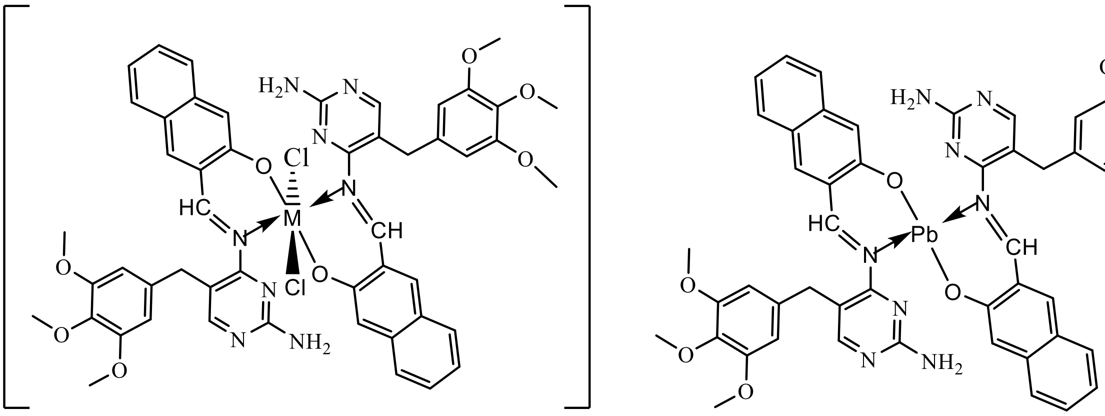
$[Fe(HL^1)_2Cl_2]Cl$

$[Fe(HL^2)_2Cl_2]Cl$

$[Mn(HL^2)_2Cl_2]Cl$

Figure 5. The suggested structures for $Mn(II)$ and $Fe(III)$ complexes incoporating TMP- Schiff base ligands, HL^1 and HL^2, which are generated from 2-hydroxybenzaldehyde and phenylmethanal.

By reacting M=Mn(II),Co(II),Ni(II),Cu(II),Zn(II),Cd(II) and [Pd(II) using Schiff base [(E)-1-((2-amino-5-(3,4,5-trimethoxybenzyl)pyrimidin-4-ylimino)methyl)naphthalen-2-ol (HL). Abdalsahib and his colleagues have synthesized novel ligand complexes. Except for complex Pd, whose geometry is square and planar, elemental and the spectral studies demonstrate a six-coordinate of complexes and validate the association of metal ions and Schiff base. Good antibacterial and antifungal properties were demonstrated by the synthesized compounds (Figure6) [29].



M= Mn(II), Co(II),Ni(II), Zn(II), and Cd(II).

Figure 6. The proposed structure formula for complexes.

Shalini and his associates used bis(benzyl)ethylenediamine as a precursor in the template process to create irregular macrocyclic complexes of $Mn(II), Co(II), Ni(II), Cu(II)$, and $Zn(II)$. Every complex belongs to the $[M(L)X_2]$ type. $v(C = N)$ (azomethine) stretches' shifts have been tracked. The activity information indicates that the metal complexes are more effective than the basic ligand, which helps identify the ligands' donor locations. Effective broad spectrum antibacterial action was demonstrated by the $[M(L)X_2]$ complexes. antibacterial action *in vitro* against isolates of bacterium that are harmful to humans that the spectrum of antibacterial activity for G+ and G- is only improved when metal chlorides and TMP complex are combined. The synthesized macrocyclic $[M(L)X_2]$ (Figure 7) [30] must be based on the results.

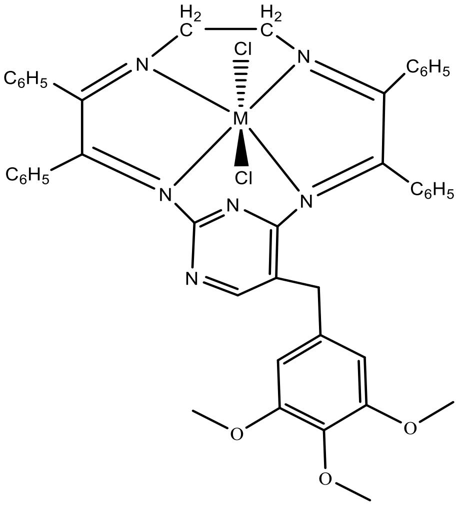
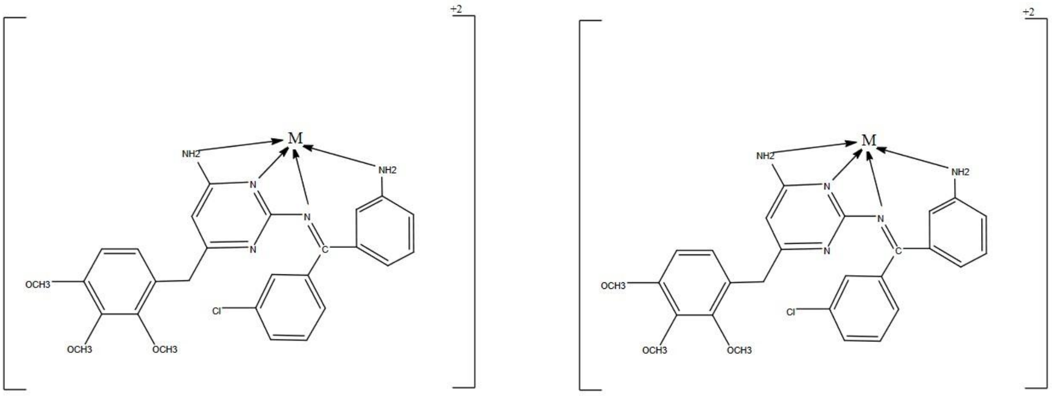


Figure 7. Suggested structure of the complexes.

(2E,4E,8E,10E)-3,4,9,10-tetraphenyl-13-(3,4,5-trimethoxybenzyl)-2,5,8,11-tetraaza-1(2,6)-pyridinacycloundecaphane-2,4,8,10-tetraene M:(Mn((II),Co(II),Ni(II),Cu(II) andZn(II).

Zaidan with his colleagues synthesized and studied the Schiff base complexes Co ((IΆ), Mn (ΆΆ), Fe (ΆΆ), Cu (ΆΆ), Ni (ΆΆ), and Zn (ΆΆ) generated from TMP and 2'-amino-4-chlorobenzophenone. Elemental testing revealed the compounds' octahedral and square planer geometries, while the solution electronic spectrum study indicates the synthesized complexes' stoichiometry. In contrast to the uncoordinated ligand [TMAB], the produced metal complexes demonstrated increased efficacy against the screened bacterial (*Escherichia coli* and *S aureus*) and fungal (*Aspergillus niger*, *Aspergillus flavus*, *Trichophyton*, *Pencillium spp.*and *Candida albicans*) strains (Figure8)[31].



(a) (b)

Figure 8. The proposed structure for complexes. (a): M= Mn, Co, Cu, the (b): M= Ni, Zn, Cd.

Garba and his colleagues used a variety of physic-chemical approaches to build and analyze chelate compounds of Mn (II), Fe (III), Co (II), and Ni (II) using Schiff base ligands generated out of TMP along with Cyclohexanone. For each belonging to the complexes, a six coordinated octahedral symmetry have been suggested. The antibacterial activity of the Schiff base ligand and its complexes was evaluated against a few pathogenic microbial isolates and contrasted with that of the parent medication. The following pattern was evident in the antibacterial activity results: Parent medicines > Schiff base ligands > metal complexes. This points to the possibility of broad-spectrum antibacterial drugs. The trend in antibacterial capabilities among the complexes are due to the M-Cl link, according to computational investigations (Figure 9) [32].

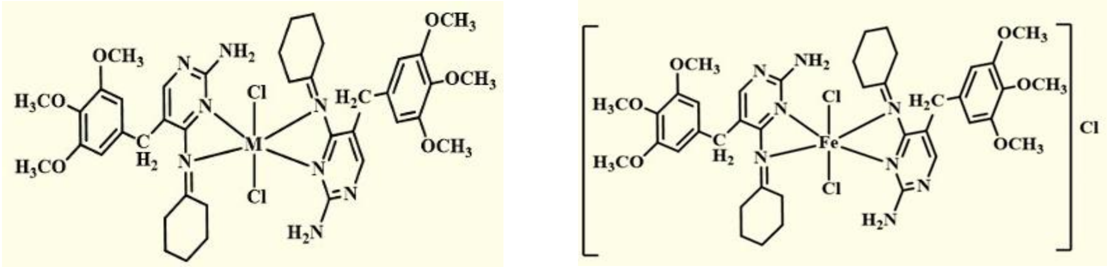
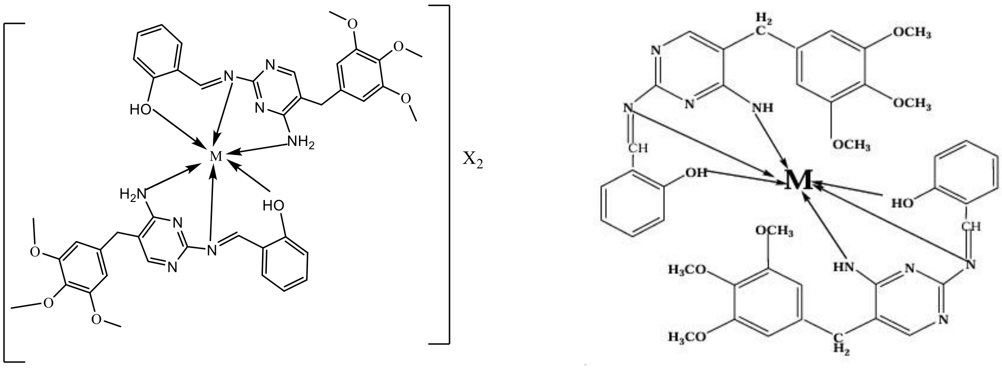


Figure 9. Structure of the metal complexes, (a): $M = Mn(II), Co(II), Ni(II),$ (b): $M = Fe(III)$.

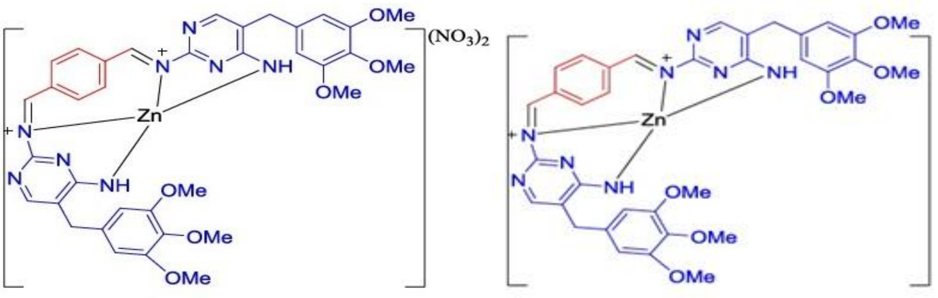
Using equal amounts of ortho hydroxybenzaldehyde and TMP as a ligand, Abed and her colleagues created a novel Schiff base (o-hydroxy benzylidene TMP) by condensation reaction. The reaction with zinc and manganese salts was then utilized to create novel complexes. In the natural media, the produced compounds were $[M(OHTMP)_2]X_2$, and within the basis medium, they were $[M(OHTMP)_2\text{-}H], M = Zn, Mn, OHTMP = o - hydroxy\ benzylidene\ TMP, X = CH_3COO, NO_3,\ \ Cl_2$). For these compounds, an octahedral geometry has been proposed. The produced ligand in addition complexes were practiced tested for their biological activities in against G+ (*S aureus*) and G- (*Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella spp.*) bacteria. The ligand and complexes' antibacterial qualities outperformed the TMP's (Figure 10)[33].



(a) (b)

Figure 10. Complexes formula in, a: Neutral medium, b: basic medium.

Ahmed and his colleagues synthesized and identified some novel compounds of zinc (II), cadmium (II), and mercury (II) using ligands (terephthalate and TMP). Several physicochemical methods were used to identify the resultant compounds. In addition to the molar electrical conductivity results of the complexes formed in a neutral enviroment confirming that they are electrolytes in a solvent, the resultant complexes are discovered to have tetrahedral geometry around Zinc (II), Cadmium (II), and Mercury (II). DMSO with DMF in a 1:1 ratio. Non-electrolyte complexes were produced in alkaline medium. The complexes of Zn(II), Cd(II), and Hg(II) displayed tetrahedral geometry in neutral and basic media, respectively, with the general formula $[M(L_3)](NO_3)_2$ and $[M(L_3)]$. The produced ligand and complexes' antibacterial activity against microorganisms (including *Klebsiella spp., Pseudomonas aeruginosa, Escherichia coli,* and *S aureus*) was next examined. Antibacterial activity was not demonstrated by either the complexes or the ligand molecules (Figure11)[34].



$[Zn(L_3)](NO_3)$

$[Zn(L_3)]$

(a)

(b)

Figure 11. The proposed structure for Zn (II) complexes. (a): in neutral medium, (b): in basic medium.

Abdalrazaq and his colleagues create metal complexes containing different ligands using ethanedionc acid and a Schiff base, which they derived from TMP and 2,4-pentadione. The synthesized complexes were of the form $[M(L_1)(L_2)]$, in which a metallic species, is $Ni(II), Cu(II), Cr(III)$ and $Zn(II)$. The first ligand, L_1, is the $TMP((Z)-4-((4-amino-5-(3,4,5-trimetoxybenzyl\,pyrimidine-2-yl)imino)pentane-2-one)$, and the second is the ethanedioate ion (CO). Schiff base coordination is a tridentate compound with $Co, Cr,$, and Zn complexes along with a bidentate ligand with Cu and Ni complexes, according to the complexes' measured and computed infrared spectra. DFT simulations were used to examine the complexes' electronic structures, revealing a range of the energy separation between the HOMO and LUMO orbitals. The complexes' ability to interact with DNA was investigated. The antibacterial qualities of the synthesized ligand along with its formed metal complexes were assessed in opposition to G+(*B subtilis*),G- (*S aureus*) and G- *Enterobacter (E) cloacae bacterial strains*. Good antibacterial activity was demonstrated by these complexes (F.g.12)[35].

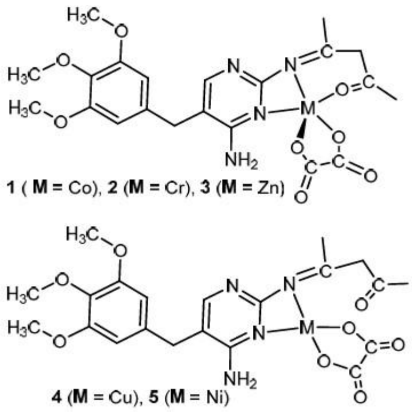


Figure 12. The proposed structure of complexes $[M(L_1)(L_2)]$.

Mishra produced and studied complexation of $Mn(II)$ and $Fe(III)$ using TMP Schiff base ligands, HL^1 and HL^2, generated by 2-hydroxy benzaldehyde and phenylmethanal. The low conductivity values indicated that the complexes are not electrolytes, but the results demonstrated that the produced substances are in their pure form due to they show distinct melting points. The acquired spectroscopic data validate the metal-ligand coordination. Fe(III) complexes exhibit greater activity than Mn(II) complexes when contrasted to the normal TMP medication, according to the results of the antimicrobial susceptibility test, MIC, and MBC (Figure 13)[36].

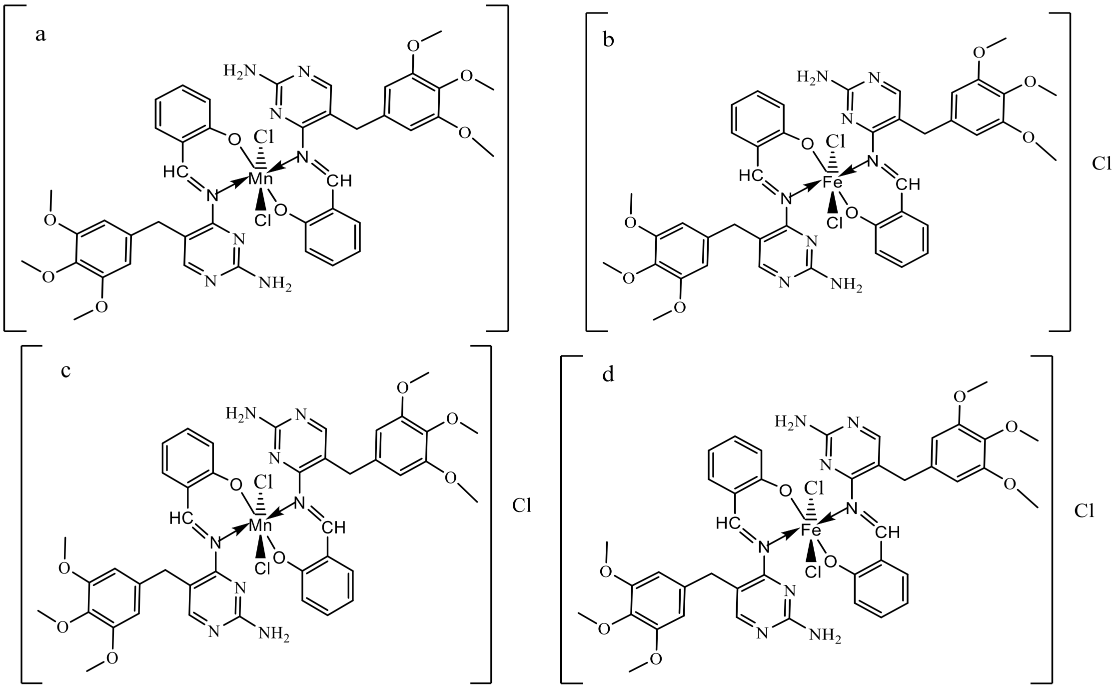
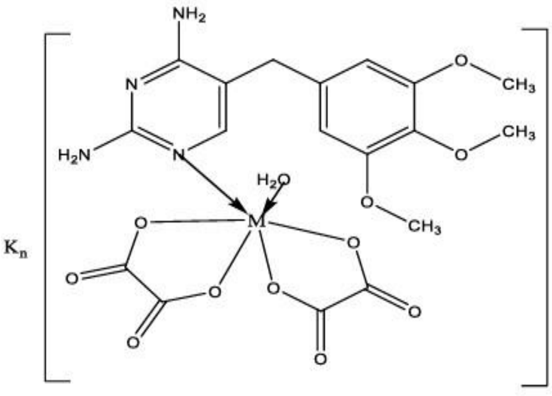


Figure 13. The proposed structure of complexes: a= $[Mn(HL^1)_2Cl_2]$, b= $[Fe(HL^1)_2Cl_2]Cl$, c= $[Mn(HL^2)_2Cl_2]Cl$, d= $[Fe(HL^2)_2Cl_2]Cl$

Complexes from TMP as a ligand

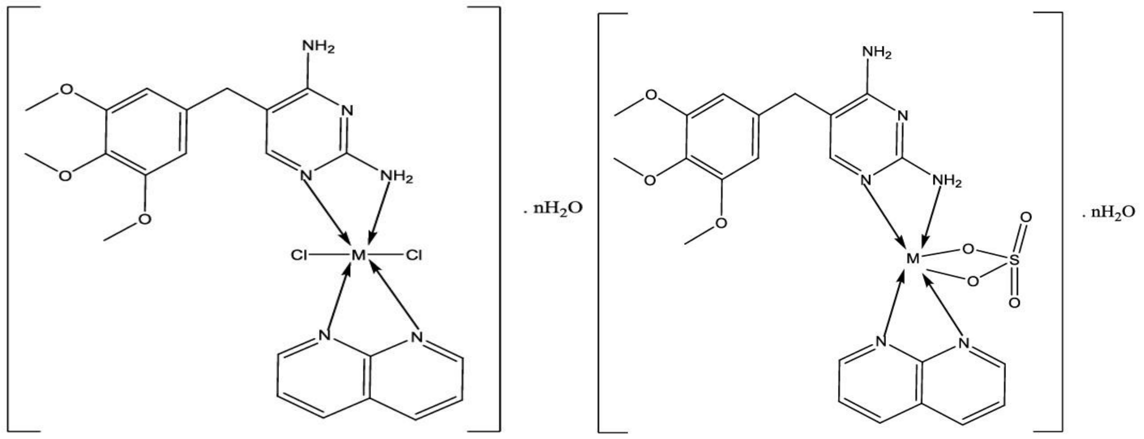
Al-Noor and Shinan conducted a study on a series of freshly synthesized mixed-metal ligand complexes, utilizing oxalic acid ($H_2C_2O_4$) as the principal ligand and (TMP) as the auxiliary ligand. The structural investigation revealed that the complexes display a six-coordinate configuration as $K_2[M(Oxalate)_2(TMP)H_2O)]$. M denotes $Mn(II), Co(II), Ni(II), Cu(II), Zn(II)$, and $K[Cr(Oxalate)_2(TMP)(H_2O)]$. The antimicrobial activity was evaluated in vitro using TMP and oxalic acid as ligands in a mixed metal ligand framework against *S. aureus* (G+), *B. subtilis* (G+), and *E. cloacae* (G-), with inhibition zones measured in millimeters (14) [37].



M= Mn(II), Co(II), Ni(II), Cu(II) ,Zn(II), n=2
M=Cr(III) , n =1

Figure 14. The proposed structure of complexes.

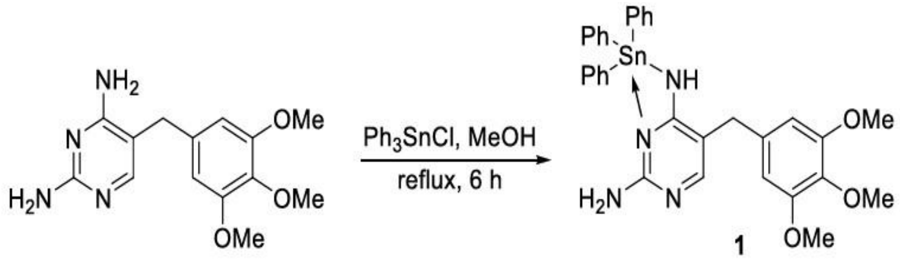
TMP and 2,2′-bipyridyl (bipy) mixed-ligand complexes that feature the formula $[M(TMP)(bipy)X]nH_2O$, where $X = Cl/SO_4$, $M = Mn(II), Co(II), Ni(II), Cu(II), Fe(II)$ and $Zn(II)$ were synthesized and described by Eugene-Osoikhia and his colleagues. As a bidentate ligand, TMP binds to the metals through the nitrogen atom of the azomethine moiety and the N atom of the pyrimidine amino group. In contrast, the diimine's nitrogen atoms allow the bipy to coordinate.. According to the results from the electronic spectra, every metal (II) complex was octahedral and monomeric. No antifungal activity was observed in the complexes and ligands, according to the antimicrobial studies; however, the mixed metal complexes' antibacterial activities showed a trend of $Mn > Zn > Cu > Fe > Co{\sim}Ni$, making[Mn (TMP)(bipy)Cl_2].$2H_2O$, the most biologically active of them. Since the maximum processes were seen at utmost concentration of 40 mg/mL (Figure15). It was likewise noted a direct relationship between antibacterial activity and concentration was observed [38].



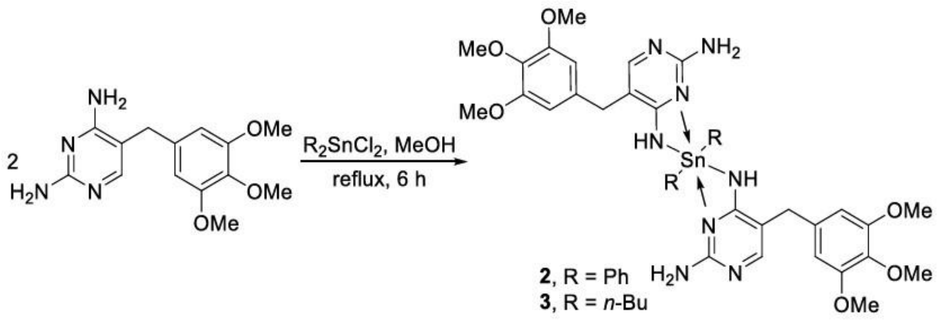
Where M = Co, Cu, Mn, Ni and n = 0, 2, Where M = Zn, Fe and n = 2, 3

Figure 15. The complexes' proposed structures are; (a): [M (TMP)(bipy)Cl$_2$].(b): [M (TMP)(bipy)SO$_4$] nH$_2$O.H$_2$O.

Emad and his colleagues had synthesized three TMP tin complexes, which were TMP combined with three distinct organo-tin compounds. At two doses (1×10^{-2}, 1×10^{-4}M), the produced compounds have demonstrated greater efficacy in suppressing bacteria like a) *B Pumilus* and b) *Candida albicans* (Figure16) [39].



a) TMP-tin complex 1



b) TMP-tin complexes 2 and 3

Figure 16. Suggested structures for the complexes a and b.

Ruthenium(*III*) , gold(*III*) , and iridium(*III*) TMP drug (TMP) complexes were synthesized and described by El-Habeeb and Refat. The TMP medication was linked as a bidentate ligand associated with the appropriate three metal cations via a duo of nitrogen atoms of -NH$_2$ amino groups. Two TMP molecules, two coordinated chlorine atoms, and one uncoordinated chlorine atom make up the octahedral geometrical structure of the compound's ruthenium(*III*) , gold(*III*) , and iridium(*III*) . Numerous bacterial species, such as *Pseudomonas aeruginosa*, *B subtilis*, *(S) aureus*, and *Escherichia coli*, have been used to study the antibacterial qualities of TMP complexes. The inhibition zone of ruthenium and iridium complexes was in the low efficiency range in comparison to that of clinically used antibiotics, and the antibacterial activity of gold(*III*) complexes was moderate. (Figure 17) [40].

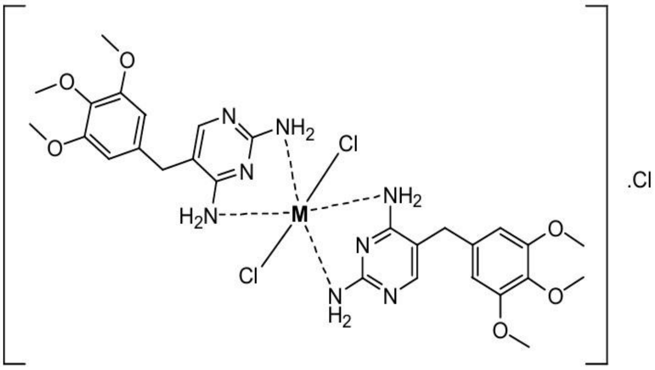


Figure 17. Ru(III), Au(III), and Ir(III)-TMP complexes and their proposed structures.

Al-Assafe and Al-Quaba have created new compounds in the $[M(TMP)(en)]X.H_2O$ and $[M(TMP)(PD)]X.nH_2O$ series, where M = Ni^{2+}, Cu^{2+}, , Zr^{4+}, Ag^{+}, Cd^{2+}, en = ethylenediamine, PD = o-phenylene, and X = Cl^{-}or No^{3-}. The arrangement of diamine ligands by nitrogen of diamine molecules was demonstrated by infrared spectra. In the meantime, TMP functioned as a bidentate ligand, attaching itself to the azomethine and pyrimidine groups via their nitrogen atoms. All compounds adopted monomeric octahedral and tetrahedral geometries, according to electronic spectra data. Broad-spectrum antibacterial activity against a variety of bacterial strains was demonstrated by the compounds and their corresponding ligands (Figure 18) [41].

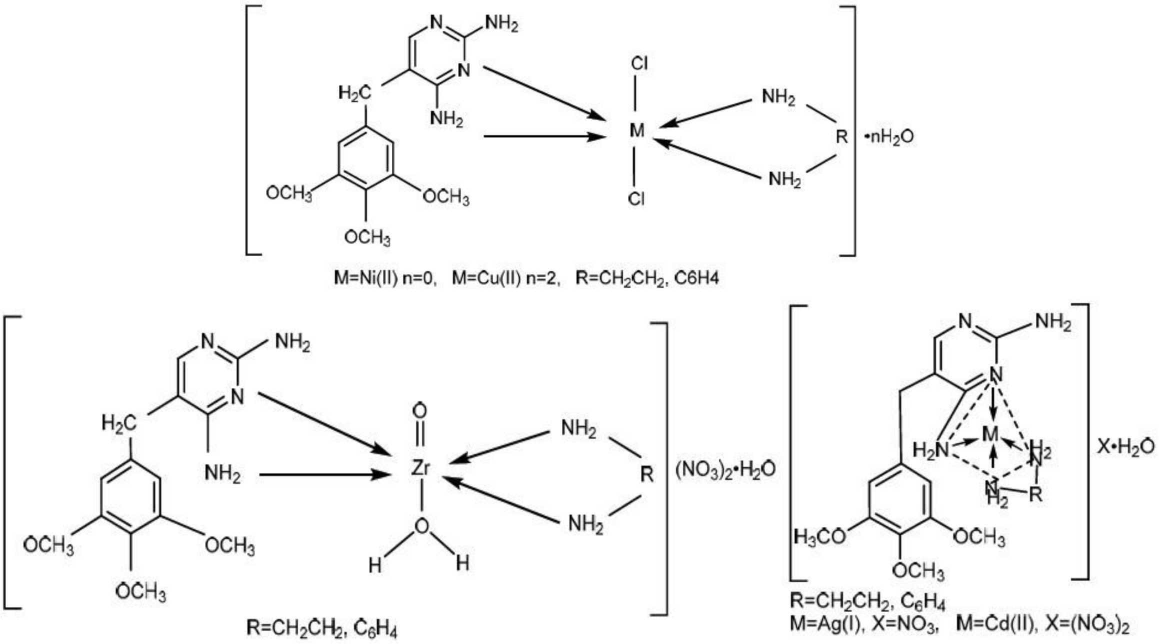


Figure 18. Suggested structure of the complexes

Conclusion

The numerous pharmacological actions of TMP, such as its antiparasitic, antibacterial, anticancer, antimalarial, antineoplastic, and antiviral properties, have stimulated interest in chemistry. Schiff base metal complexes have been extensively researched due to their biological, antifungal, and industrial uses. They have been linked to urinary tract infections and have been significant in the development of coordination chemistry.

Acknowledgments

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Conflict of Interest

The authors declare no competing interests.

References

[1] Aryee, A. A., & Han, R. (2022). A novel biocomposite based on peanut husk with antibacterial properties for the efficient sequestration of trimethoprim in solution: Batch and column adsorption studies. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 635, 128051.

[2] Abdalsahib, N. M., Numan, A. T., & Atiyah, E. M. (2018). Preparation, Characterization and Biological Activity Studies of Some Metal Complexes with New Schiff Base for Trimethoprim Ligand. Journal of Global Pharma Technology. 10(11) 340.

[3] Al-Noor, T. H., Karim, L. K. A., & Ali, F. M. (2016). Schiff Base And Ligand Metal Complexes of Some Amino Acids and Drug. LAP LAMBERT Academic Publishing.

[4] Delas Cuevas, C., Sanz, E and de la Fuente, J. (2003). Benzodiazepines: more "behavioural" addiction than dependence. Psychopharmacology, 167, 297-303.

[5] McEvoy, G. K. (Ed.). (2013). American hospital formulary service drug information. Pharmaceutical Press.

[6] Merrill Jr, A. H., & Henderson, J. M. (1990). Vitamin B6 metabolism by human liver. Annals of the New York academy of sciences, 585, 110-117.

[7] Aljeboree, A.M., Alhattab, Z.D., Altimari, U.S., Aldulaim, AKO, Mahdi, A.K., & Alkaim, AF. (2023). Enhanced removal of amoxicillin and chlorophenol as a model of wastewater pollutants using hydrogel nanocomposite: Optimization, thermodynamic, and isotherm studies. Caspian Journal of Environmental Sciences. 21: 411.

[8] Demirezen N., Tarınç D., Polat D., Çeşme M., Gölcü A., & Tümer M. (2012). Synthesis of trimethoprim metal complexes: electrochemical, thermal, DNA-binding and surface morphology studies. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy. 94; 243.

[9] Rajapakse, C. S., Martinez, A., Naoulou, B., Jarzecki, A. A., Suárez, L., Deregnaucourt, C., & Sánchez-Delgado, R. A. (2009). Synthesis, characterization, and in vitro antimalarial and antitumor activity of new ruthenium (II) complexes of chloroquine. Inorganic chemistry, 48(3), 1122-1131.

[10] Ang, W. H., Daldini, E., Scolaro, C., Scopelliti, R., Juillerat-Jeannerat, L., & Dyson, P. J. (2006). Development of organometallic ruthenium− arene anticancer drugs that resist hydrolysis. Inorganic chemistry, 45(22), 9006-9013.

[11] Lebwohl, D., & Canetta, R. (1998). Clinical development of platinum complexes in cancer therapy: an historical perspective and an update. European journal of cancer, 34(10), 1522-1534.

[12] Hartinger, C. G., Jakupec, M. A., Zorbas-Seifried, S., Groessl, M., Egger, A., Berger, W., & Keppler, B. K. (2008). KP1019, a new redox-active anticancer agent–Preclinical development and results of a clinical phase I study in tumor patients. Chemistry & biodiversity, 5(10), 2140-2155.

[13] Abdulmawjood, S., & Altamer, Z. (2024). The relationship of hypothyroidism to iron deficiency in the body. NTU Journal of Pure Sciences, 3(1).

[14] Sava, G., Bergamo, A., & Dyson, P. J. (2011). Metal-based antitumour drugs in the post-genomic era: what comes next. Dalton Transactions, 40(36), 9069-9075.

[15] Sakurai, H., Kojima, Y., Yoshikawa, Y., Kawabe, K., & Yasui, H. (2002). Antidiabetic vanadium (IV) and zinc (II) complexes. Coordination Chemistry Reviews, 226(1-2), 187-198.

[16] Kiss, T., Jakusch, T., Hollender, D., Dörnyei, Á., Enyedy, É. A., Pessoa, J. C., & Sanz-Medel, A. (2008). Biospeciation of antidiabetic VO (IV) complexes. Coordination Chemistry Reviews, 252(10-11), 1153-1162.

[17] Messori, L ., & Marcon, G. (2004). Gold complexes in the treatment of rheumatoid arthritis. Metal Ions Biological Systems. 41, 279.

[18] Caravan, P., Ellison, J. J., McMurry, T. J., & Lauffer, R. B. (1999). Gadolinium (III) chelates as MRI contrast agents: structure, dynamics, and applications. Chemical reviews, 99(9), 2293-2352.

[19] Garoufis, A., Hadjikakou, S.K., & Hadjiliadis, N. (2009). Palladium coordination compounds as antiviral, anti-fungal, antimicrobial and anti-tumor agents. Coord. Chem. Rev. 253, 1384.

[20] Orvig, C. and Abrams, M.J. (1999). Medicinal inorganic chemistry. Chem. Rev. 99, 2201.

[21] Abdulghani, A. J., &Hussain, R. K. (2015). Synthesis and Characterization of Schiff Base Metal Complexes Derived from Cefotaxime with 1H-indole-2,3-dione (Isatin) and 4-N,N-dimethyl-aminobenzaldehyde. Open J. Inorganic Chem. 5, 83.

[22] Cozzi, P. G. (2004) Metal-Salen Schiff base complexes in catalysis: practical aspects. Chem. Soc. Rev. 33, 410.

[23] Abood. H. S. 1, Ramadhan. U. H., &Hamza, H. (2020). Synthesis and anti-inflammatory activity study of Schiff bases complexes. Bio chem. Cell. Arch. Vol. 20(2) 5627.

[24] Talal, R. (2024). Synthesis of New polymers of Triazole Derivatives. NTU Journal of Pure Sciences, 3(3).

[25] Joshi, S., Pawar, V., & Uma, V. (2010). Antibacterial properties of Mn (II), Co (II), Ni (II) and Zn (II) complex of derived from Schiff base trimethoprim. Der Pharma Chemica, 2, 329-336.

[26] Li, X., Jiang, J. H., Xiao, S. X., Gu, H. W., Li, C. H., Ye, L. J., & Li, Q. G. (2014). Synthesis, thermodynamic properties and BSA interaction of a new Valen Shiff base derived from o-vanillin and trimethoprim. Thermochimica Acta, 575, 291-299.

[27] Numan, A. T., Atiyah, E. M., Al-Shemary, R. K., & Abd_Ulrazzaq, S. S. (2018). Composition, characterization and antibacterial activity of Mn (II), Co (II), Ni (II), Cu (II) Zn (II) and Cd (II) mixed ligand complexes Schiff base derived from trimethoprim with 8-hydroxy quinoline. In Journal of Physics: Conference Series (Vol. 1003, No. 1, p. 012016). IOP Publishing.

[28] Ndahi, N. P., Garba, H., Waziri, I., Osunlaja, A. A., & Putaya, H. A. (2018). Complexes of Mn (II) and Fe (III) with Schiff bases derived from trimethoprim with salicyldehyde and benzaldehyde as potential antimicrobial agents. Nigerian Journal of Pharmaceutical and Biomedical Research, 3(1).

[29] Abdalsahib, N. M., Numan, A. T., &Atiyah, E. M. (2018). Preparation, Characterization and Biological Activity Studies of Some Metal Complexes with New Schiff Base for Trimethoprim Ligand. Journal of Global Pharma Technology. 10(11) 340.

[30] Shalini, A. S., Amaladasan, M., Prasannabalaji, N., Revathi, J., & Muralitharan, G. (2019). Synthesis, characterization and antimicrobial studies on 13-membered-N6-macrocyclic transition metal complexes containing trimethoprim. Arabian Journal of Chemistry, 12(7), 1176-1185.

[31] Zaidan, B. A. H., Majeed, N. M., Al-Shemary, R. K., & Numan, A. T. (2019). Synthesis of some Schiff base metal complexes involving trimethoprim and 2'-amino-4-chlorobenzophenone: Spectral, thermal, DNA Cleavage antimicrobial, antifungal and Cytotoxic activity studies. Journal of Pharmaceutical Sciences and Research, 11(2), 618-626.

[32] Garba, H., Yakasai, J. B., Waziri, I., & Bisiriyu, I. O. (2020). Transition Metal Complexes of Schiff Base Ligand Derived from Trimethoprim with Cyclohexanone: Synthesis, Characterization, Antimicrobial and Computational Studies. Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423), 4(5) 63.

[33] Abed, R. R., Mohammed, A. S., & Ahmed, F. J. (2021). Synthesis and diagnoses of new metal ions complexes derived from trimethoprim Schiff bases. Research Journal of Pharmacy and Technology, 14(9), 4963-4968.

[34] Ahmed, F. J., AbdAlqader, B., Haddad, R. A., Abed, R. R., & Saleh, M. Y. (2022). Preparation and diagnosis of Zn (II), Cd (II) and Hg (II) complexes with Schiff base ligand derived from trimethoprim. Egyptian Journal of Chemistry, 65(10), 359-366.

[35] Abdalrazaq, E., Jbarah, A. A. Q., Al-Noor, T. H., Shinain, G. T., & Jawad, M. M. (2022). Synthesis, DFT calculations, DNA interaction, and antimicrobial studies of some mixed ligand complexes of oxalic acid and Schiff base trimethoprim with various metal ions. Indonesian Journal of Chemistry, 22(5), 1348-1364.

[36] Ndahi, N. P., Garba, H., Waziri, I., Osunlaja, A. A., & Putaya, H. A. (2018). Complexes of Mn (II) and Fe (III) with Schiff bases derived from trimethoprim with salicyldehyde and benzaldehyde as potential antimicrobial agents. Nigerian Journal of Pharmaceutical and Biomedical Research, 3(1).

[37] Al-Noor, T. H., & Shinan, G. T. (2017). Synthesis and characterization of mixed-ligand complexes of oxalic acid and trimethoprim with Mn (II), Co (II), Ni (II), Cu (II), Zn (II), and Cr (III) ions: and antimicrobial activities. Research Journal of Pharmaceutical, Biological and Chemical Sciences, 8(3), 1375-1381.

[38] Eugene-Osoikhia, T. T., Ojeyemi, S. A., Akong, R. A., Oyetunde, T., Onche, E. U., & Ayeni, F. (2021). Synthesis, characterisation and antimicrobial studies of metal (II) complexes of trimethoprim and 2, 2'-bipyridin heterocycle. Niger. Res. J. Chem. Sci, 9(1), 273-295.

[39] Emad, Y., Salam, M., Rahimi, Y., Muna, B., Israa, S., Dina, A., & Anaheed, Y. (2023). Anti-bacterial activity for trimethoprim Cefixime and trimethoprim tin and its complexes. Journal of Biotechnology Research Center, 17(1).

[40] El-Habeeb, A. A., & Refat, M. S. (2024). Synthesis, spectroscopic characterizations and biological studies on gold (III), ruthenium (III) and iridium (III) complexes of trimethoprim antibiotic drug. Bulletin of the Chemical Society of Ethiopia, 38(3), 701-714.

[41] Al-Assafe, A. Y., & Al-Quaba, R. A. M. S. (2024). New Series of Ni (II), Cu (II), Zr (IV), Ag (I), and Cd (II) Complexes of Trimethoprim and Diamine Ligands: Synthesis, Characterization, and Biological Studies. Indonesian Journal of Chemistry, 24(3), 812-821.