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Biological Activity of Metal Complexes of Sulfamethoxazole and Its Derivatives: A Literature Review

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Abstract

Sulfamethoxazole and its derivatives are commonly utilized in the pharmaceutical and medicinal industry due to their biological and pharmaceutical activities, including anti-tubercular, anti-fungal, anti-cancer, anti-bacterial, and herbicidal activities. This review presents the latest and most promising studies related to synthesizing organic derivatives of sulfamethoxazole and their drug-metal complexes and the biological activity associated with these complexes. Some organic drugs, including sulfamethoxazole, exhibit toxicological and pharmacological properties that can be administered in the form of metal complexes. Many researchers have synthesized organic ligands derived from sulfamethoxazole in the forms of Schiff bases and azo compounds, which exhibited higher biological and industrial properties when compared to sulfamethoxazole alone. One of the essential features that make Schiff base more desirable when used for coordination complexation is that it possesses the ability to coordinate with the metal ions via forming chelating; ring makes them very effective in clinical and analytical applications and represent the latest and most promising studies and relate to synthesizing organic derivatives of sulfamethoxazole and their drug-metal complexes, as well as the biological activity associated with these complexes.

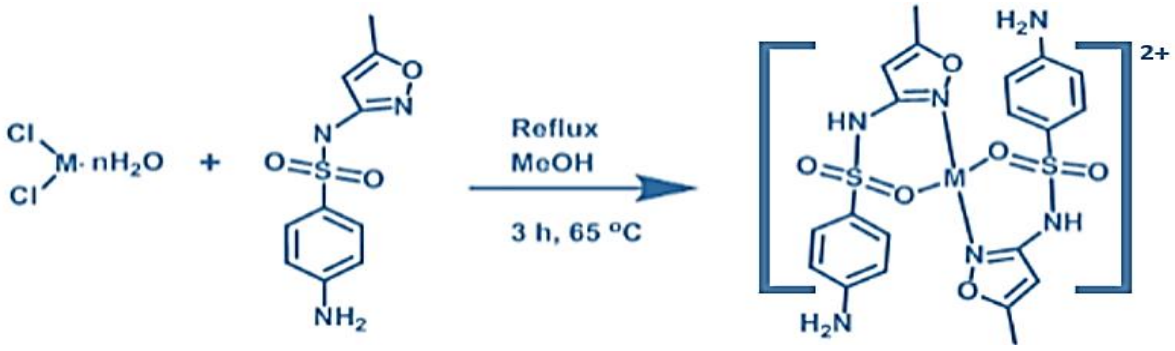
Keywords: Sulfamethoxazole, metal-complexes, biological activity, sulfa-drug, coordination chemistry.

1. Introduction

Sulfamethoxazole and its derivatives belong to sulfonamides, structural para-aminobenzoic acid (PABA) analogs. This type of molecule is commonly utilized in the

pharmaceutical and medicinal industry due to its biological effectiveness (1-3). One of the critical aspects of the sulfamethoxazole molecule is preventing dihydrofolic acid, the molecule that ensures the survival of bacteria, from being formed. Schiff bases are usually synthesized from reacting sulfamethoxazole with a particular aldehyde or ketone (4-6). Schiff bases play an essential role in coordination chemistry as they are used as chelating agents in the form of Schiff base-metal complexes with a wide range of clinical, analytical, and biological uses (7). In terms of biological activities, they exhibit anti-tubercular activities, anti-fungal, anti-cancer, anti-bacterial, and herbicidal activities (8,9). Furthermore, promoting burns' rapid healing in animals and humans is linked to some metal complexes of Schiff bases derived from sulfamethoxazole (10-12). It is worth mentioning that sulfonamides were used systematically as chemotherapeutic agents to prevent bacterial infections in humans (4,13). Sulfamethoxazole is very efficient in growth inhibition of both gram-negative and gram-positive bacteria with a competitively binding to dihydropteroate synthetase that is responsible for converting *p*-aminobenzoic acid to dihydropteroate (14,15). The latter is the tetrahydrofolic acid precursor essential for synthesizing nucleic acids. One of the mechanisms of action sulfonamides are responsible for is to block the cross-membrane transportation of glutamic acids to synthesize folic acid (17-19).

Metal-organic complexes have been among the most interesting fields in the last two decades for various applications in molecular adsorption, catalysis, nonlinear optics, magnetism, and molecular sensing, mainly contributing to their intriguing structures and novel topologies (6). Nevertheless, some organic drugs, including sulfamethoxazole **Scheme 1**, which exhibit toxicological and pharmacological properties, can be administered in the form of metal complexes (27-30). These organic molecules can act as ligands in preparing metal-drug complexes, which are essential in biochemistry and coordination chemistry (13,20,21). This review presents the latest and most promising studies related to synthesizing organic derivatives of sulfamethoxazole and their drug-metal complexes and the biological activity associated with these complexes.



Scheme 1. General reaction of synthesizing sulfamethoxazole-metal complexes.

2. Materials and Methods

2.1. Sulfamethoxazole metal complexes

2.1.1. Drug complexes of sulfamethoxazole with Au(III), Ru(III), and Pt(IV)

Some metal complexes of Au(III), Ru(III), and Pt(IV) were prepared with sulfamethoxazole and characterized utilizing different techniques, such as thermal analysis, elemental analyses, ^{1}H-NMR, IR, UV, molar conductivity, magnetic moment and XRD analyses (22). The complexes showed high surface uniformity, confirmed by the X-ray diffraction patterns and SEM images. Transmission electron microscopy (TEM) pictures, however, showed a particle size of 100–200 nm for the solid form of the prepared complexes. IR spectroscopic data suggested that the ligand behaves as bi-dentate with the oxygen of sulfonyl and nitrogen of amido group coordinated to the metal ions. The Au(III) and Ru(III) complexes showed an electrolytic property. The prepared complexes exhibited high thermal stability in dynamic air according to the TG and DTG experiments. Moreover, the biological activity of the complexes exceeded that of ligand alone in terms of antifungal and antibacterial activity when they were tested against various microorganisms, with the ultimate activity of the Pt (IV) complex. The chemical structure of the prepared complexes was proposed to be in the octahedral geometry except for the Au (III) complex, which was proposed to be square planner geometry, as illustrated in **Figure 1** (22).

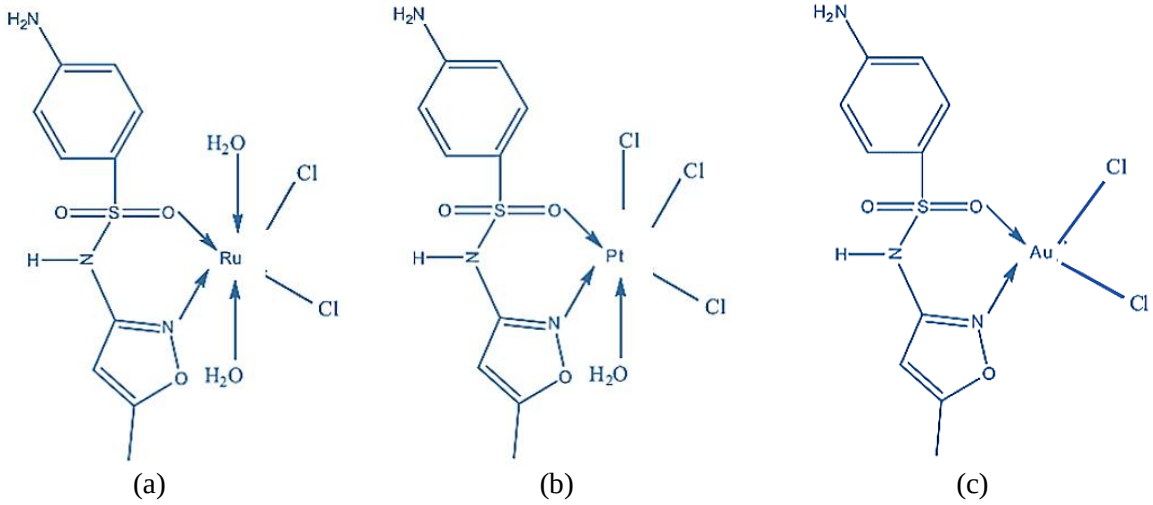


Figure 1. Chemical structures of sulfamethoxazole complexes with (a) Ru(III), (b) Pt(IV), and (c) Au(III) (22).

2.1.2. Drug complexes of sulfamethoxazole with Ca(II), Zn(II) and Au(III)

New metal complexes of Zn (II), Ca (II), and Au (III) were prepared three with sulfamethoxazole. Electronic spectra, 1H-NMR, IR spectroscopic techniques, molar conductance, and elemental analysis were used to characterize the prepared complexes (13). The coordinated ligand showed some shifting in the vibrational bands of the IR spectra, specifically the isoxazole (C=N) and sulfonamide (-NH and SO_2) groups linked to the metals. The isoxazole nitrogen and sulfonyl oxygen were the coordination sites of Zn(II) and calcium(II) complexes. The prepared complexes were indicated with the chemical formula $[Au(SZ)(Cl)_2]$. Cl,

[Zn(SZ)(Cl)$_2$].2H$_2$O, and [Ca(SZ)(Cl)$_2$)].8H2O with chemical structures that are illustrated in **Figure 2**. While the complexes of Zn(II) and Ca(II) are non-electrolyte, the Au(III) exhibited electrolytic properties as the molar conductance data reveled. The prepared complexes were morphologically studied using transmission electron microscopy, scanning electron microscope, and X-ray powder diffraction techniques to examine the potential nano-scale morphology. (HepG-2) cells of hepatocellular carcinoma and (HCT-116) cells of colon carcinoma were used to study the anticancer behavior of the complexes, which showed that Au(III)-complex exhibits a perfect activity (13).

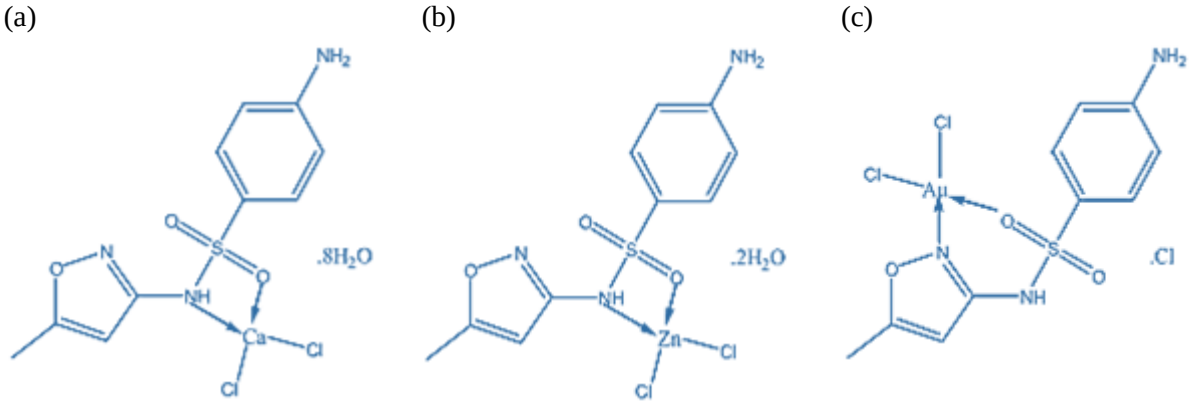


Figure 2. Chemical structures of (a) [Ca(SZ)(Cl)$_2$].8H$_2$O, (b) [Zn(SZ)(Cl)$_2$].2H$_2$O, and (c) [Au(SZ)(Cl)$_2$].Cl complexes (13).

3. Results and Discussion

3.1. Mixed-ligand complexes of sulfamethoxazole

3.1.1. Silver complexes of sulfathiazole and sulfamethoxazole

Two types of silver(I) complexes were synthesized and spectroscopic characterized with sulfamethoxazole (Ag-SFT) and sulfathiazole (Ag-SFM) with 1:1 molar composition and coordination formula [Ag($C_{10}H_{10}N_3O_3S$)] for Ag-SFM complex and [Ag($C_9H_8N_3O_2S_2$)] for Ag-SFT complex which deduced according to mass spectrometric and elemental analysis (3). The ligands coordinated to silver in both complexes by the N-atom of sulfonamide groups, as the ^{1}H-^{15}N NMR data showed. X-ray diffraction data of the crystal structure of Ag-SFT demonstrate a dimeric conformation as two ligands are bridged by Ag(I) ions, as illustrated in **Figures 3** and **4**. The prepared complexes exhibited high activity against Gram-negative strains of bacteria in the DMSO solution. Argentophilic interaction was shown in the Ag-SFT complex where the distance of Ag ... Ag was 2.89 Å with an inversion center in the middle of this interaction regarding the dimer of a Centro symmetric structure.

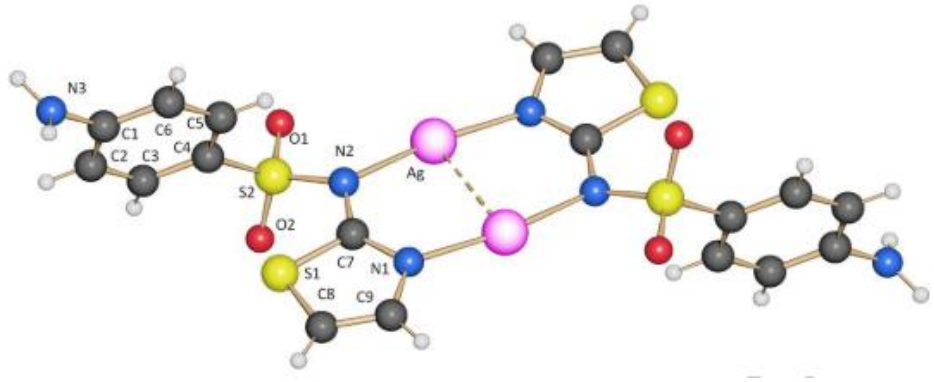


Figure 3. Structure model of dimeric Ag-SFT.

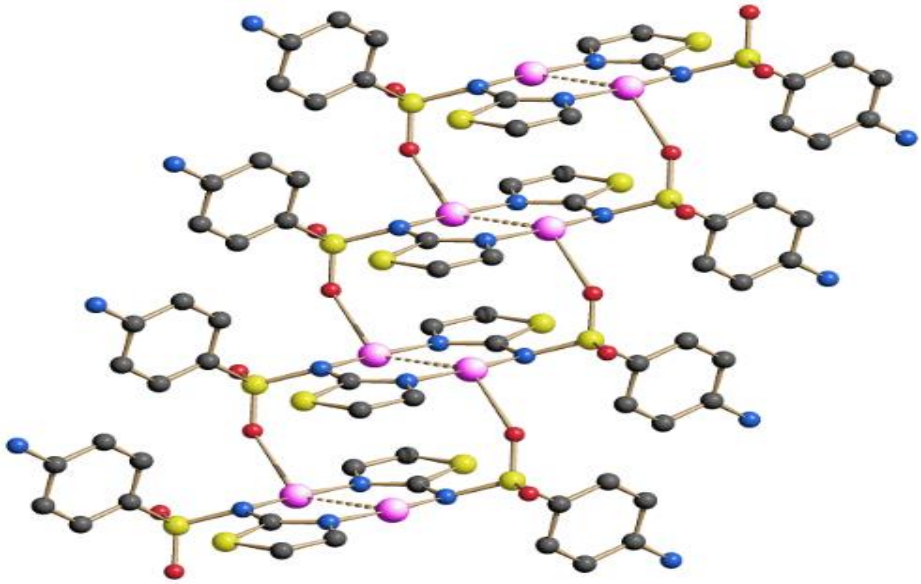


Figure 4 Structure model of Ag-SFT polymeric chain that formed through Ag-O bonding.

3.1.2. Drug-metal complexes of mixed trimethoprim-sulfamethoxazole

Complexes of sulfamethoxazole (SMX) and Trimethoprim (TMP) in forms of mixed drug metal (II) complexes were synthesized by percentage metal as well as characterized those using electronic and infrared spectroscopies, melting points, conductance measurements, room temperature magnetic moment (9). The general formula [M(TMP)(SMX)X].nH_2O was proposed for the resulting complexes according to the metal analysis, where M = Zn, Co, Ni, Fe, Mn, and Cu and X= SO_4 or Cl_2. According to infrared analysis, SMX ligand is coordinated to the metal by amino nitrogen and sulphone oxygen atoms, whereas TMP ligand is coordinated through azomethine and amino nitrogen atoms. All the prepared metal complexes have an octahedral geometry and magnetically dilute according to the electronic spectra and room temperature magnetic moment. Moreover, all the prepared complexes are confirmed to be covalent according to the molar conductance in DMSO. In terms of the bioactivity of the prepared complexes, all of the complexes were in-vitro studied for the antimicrobial activity. The metal complexes of SMX and TMP, except the Ni (II) complex, exhibited a broad-spectrum of antimicrobial activities

against *Candida albicans, Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas spp, Proteus mirabilis, Escherichia sp, and Bacillus spp*. (9). **Figure 5 (a)** and **(b)** is representing the chemical structures of the prepared complexes where M is (a) Mn and Ni, (b) Zn, Co, Cu.

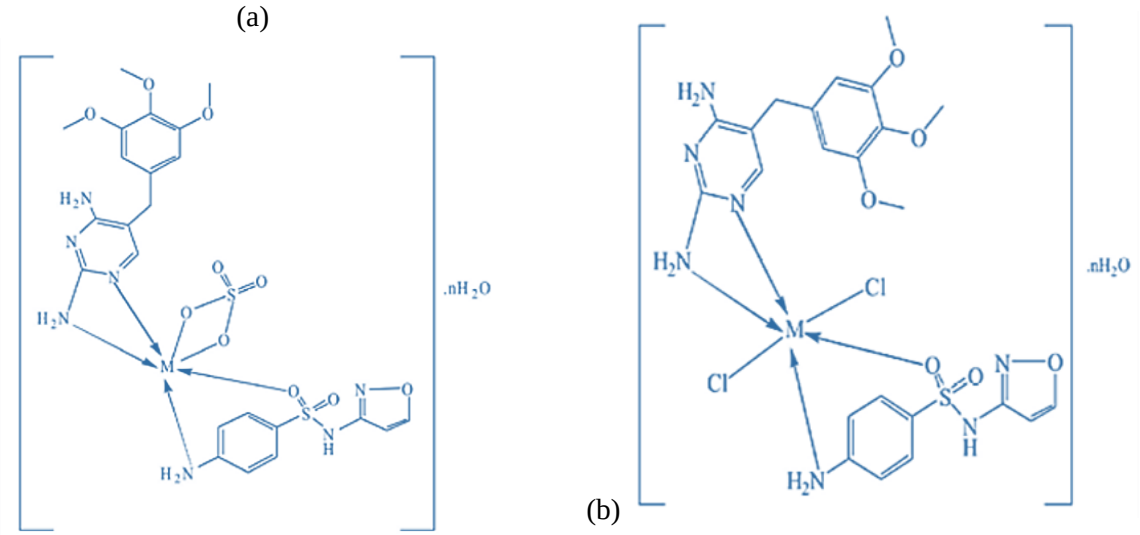


Figure 5. Chemical structures of the complexes, M is (a) Mn and Ni, and (b) Zn, Co, and Cu (9).

3.1.3. Mixed-ligand complexes of N,N- donors heterocycles and sulfamethoxazole with metal (II) ions

Two different mixed ligands complexes of N, N-donor heterocyclic, and sulfamethoxazole (SMX) were prepared, where the heterocyclic includes "bipy" 2,2′-bipyridine and "phen" 1,10-phenanthroline. The chemical composition of the complexes is [M(SMX) (bipy) X]. nH2O and [M(SMX)(phen)X].nH_2O, where M= Co(II) , Cu(II), Fe (II), Zn(II), and Mn (II), and X= Cl_2 or SO_4 (16). The prepared complexes were characterized using a variety of physical and spectroscopic techniques. While the SMX coordinated as a bi-dentate ligand linked to the metal from the nitrogen of sulfonamide and oxygen of sulfonyl groups, the heterocyclic linked through nitrogen atoms of diamine in the form of bi-dentate ligand according to the IR data. The geometrical structure of the prepared complexes was proposed as an octahedral and monomeric structure as deduced from the electronic spectroscopic data, as illustrated in **Figure 6**. Some strains of microorganisms, including *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans*, *Aspergillus niger*, *Escherichia coli*, and *Bacillus subtilis*, were used to conduct an *in vitro* studies to test the anti-microbial activates of the prepared complexes. The study showed that metal complexes of SMX-phen exhibit better biological activity than the other heterocyclic with inhibition zones that ranged between 28 and 10 mm. The superior activity of the complexes might be attributed to the large aromatic system that supports higher lipophilic properties, which will enhance the complex's penetration through the cell membrane and promote intracellular interactions that cause the microorganisms' death (16).

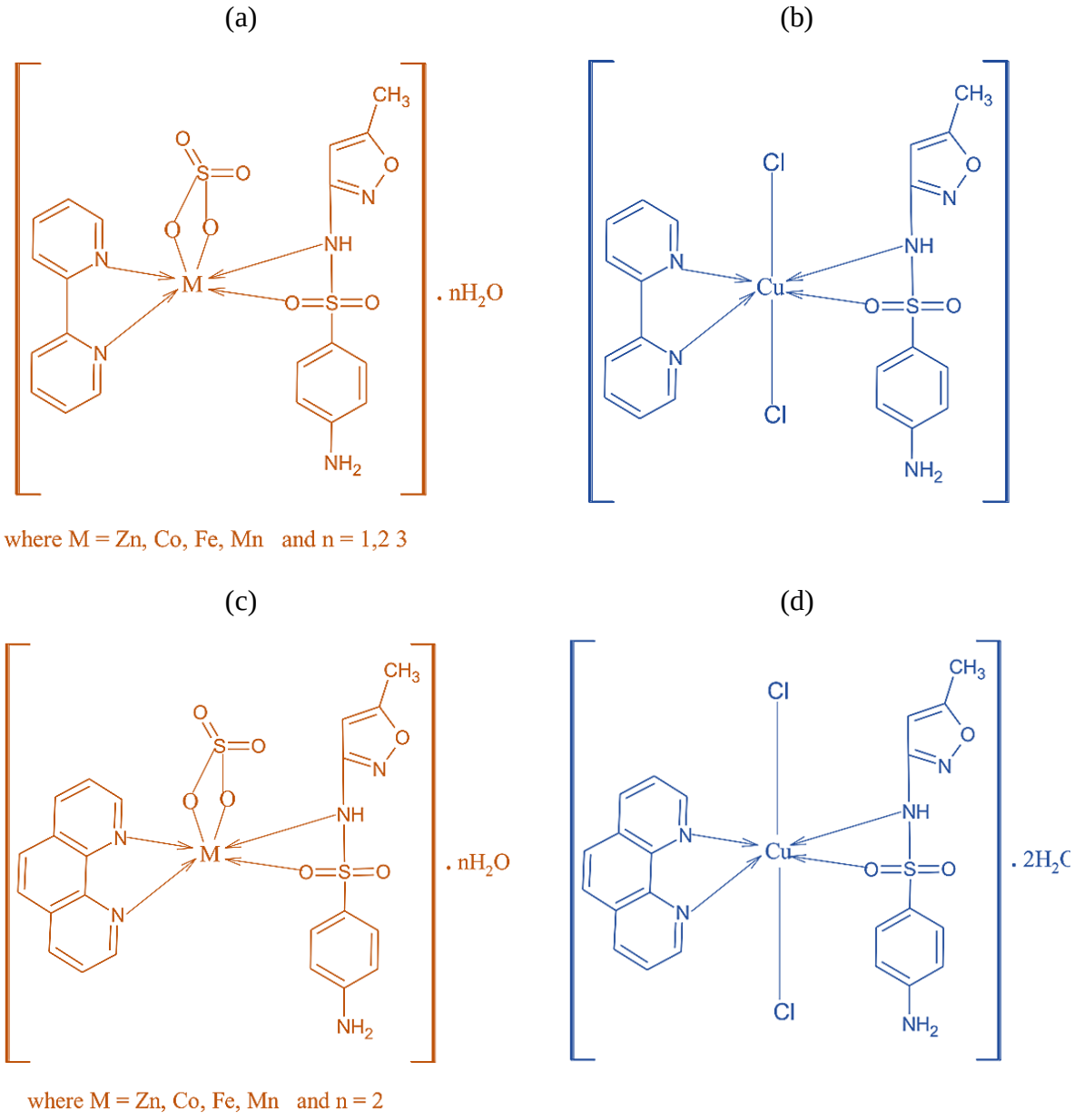


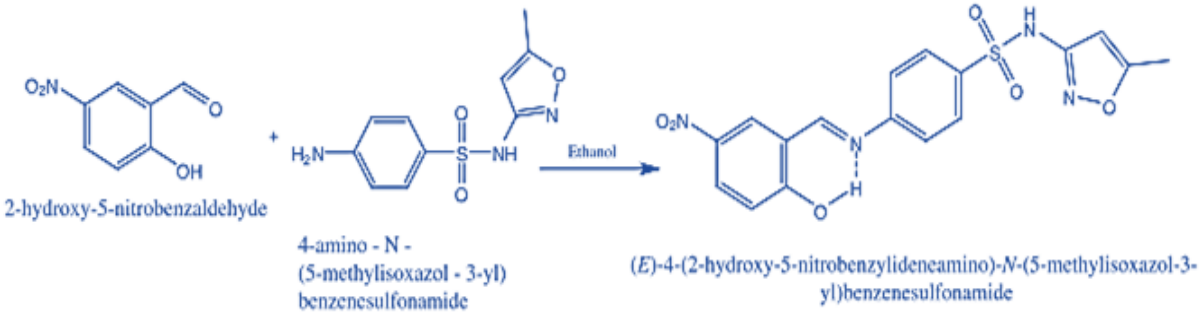
Figure 6. Proposed chemical structure of (a) $[M(SMX)(bipy)SO_4].nH_2O$, (b) $[Cu(SMX)(bipy)Cl_2]$, (c) $[M(SMX)(phen)SO_4].nH_2O$, and (d) $[Cu(SMX)(phen)Cl_2].2H_2O$ (16).

3.2. Metal complexes of sulfamethoxazole derivatives

3.2.1. Copper complex of a novel sulfamethoxazole derivative in form of Schiff base

A novel Schiff base ligand bidentate with O and N donor atoms was synthesized by reacting 5-nitro salicylaldehyde with sulfamethoxazole. The synthesized ligand was characterized using FT-IR, ^{1}H-NMR, ^{13}C-NMR, and elemental analysis. This ligand prepared the copper complex by reacting one equivalent of the metal in copper acetate and two equivalents of the ligand in a DMF-ethanolic mixture solution (23). The complexes were characterized using

single-crystal X-ray diffraction, magnetic moment, EPR, molar conductance, FT-IR, and UV techniques. According to the crystal structure of the complexes with an octahedral geometry, two DMF solvent molecules acted as ligands at the axial positions, as illustrated in **Scheme 2** and **Figure 7**. According to the molar conductance data, the prepared complex exhibits non-electrolytic properties. Anti-bacterial and anti-fungal studies were conducted on the Schiff base and its metal complex against different microorganisms. The prepared ligand and its copper complex were in-vitro tested regarding their cytotoxicity, which was conducted on MDA–MB–231 and HCT-116 lines of human tumor cells. According to the cytotoxicity investigation, the complex exhibits much higher activity towards MDA–MB–231 than carboplatin and cisplatin (23).



Scheme 3. Synthesis reaction of the Schiff base ligand (23).

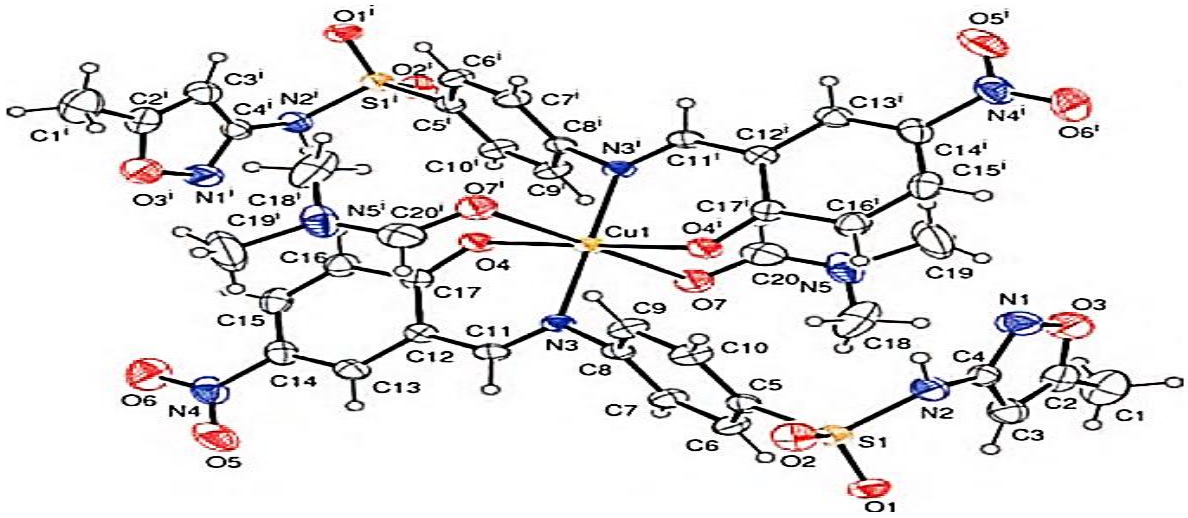


Figure 7. The ORTEP crystalline structure of $[Cu(L)_2(DMF)_2]$ (23).

3.2.2. Complexes of Schiff base that derived from sulfamethoxazole and furfural with Co(II) and Ni(II) ions

Complexes of Co(II) and Ni(II) with a Schiff base derived from furfural and sulfamethoxazole were prepared and characterized using various spectroscopic techniques. According to the spectral data, the Schiff base ligand was linked to the metal from the azomethine's nitrogen atom and the furfural moiety's oxygen atom in the form of the bi-dentate ligand with a Tetrahedral geometry. When tested against microorganisms, including bacteria and fungi, the

complexes exhibited much higher activity than the Schiff base alone. The prepared complexes showed good thermal stability with non-electrolytic behavior, and the proposed chemical structures of the prepared complexes are shown in **Figure 8** (2).

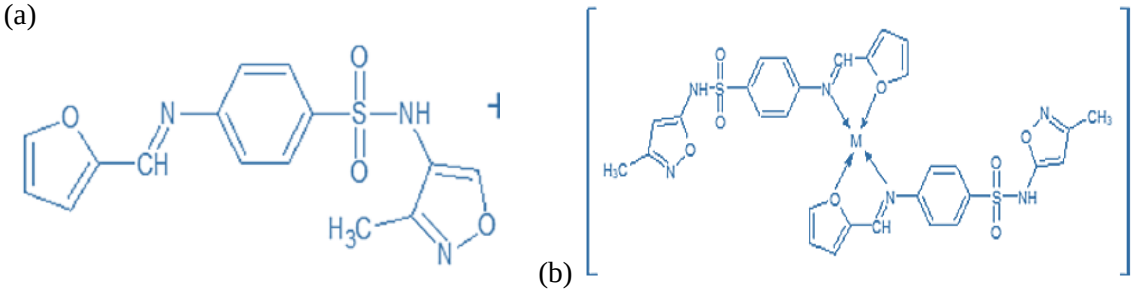


Figure 8. Chemical structure of the (a) the prepared Schiff base, and (b) the metal complex (2).

3.2.3. Complexes of sulfamethoxazole derivatives with Cu(II), Mn(II) and Zn(II) metal ions

The 3-nitro benzophenone sulfamethoxazole and acetophenone sulfamethoxazole were synthesized by a reaction of sulfamethoxazole with two different ketones. The synthesized derivatives are used as ligands to prepare metal complexes with Cu(II), Mn(II), and Zn(II) ions in aqueous alcohol with a 1:1 molar ratio. The general formula $[M(L)(Cl)_2(H_2O)].H_2O$ was proposed for the resulting complexes with an octahedral geometry that was suggested according to the characterization techniques for the prepared complexes as illustrated in (a) and (b). According to the characterization techniques, the researcher proposed an octahedral geometry for all the complexes, as described in **Figure 9 (a)** and **(b)** (24).

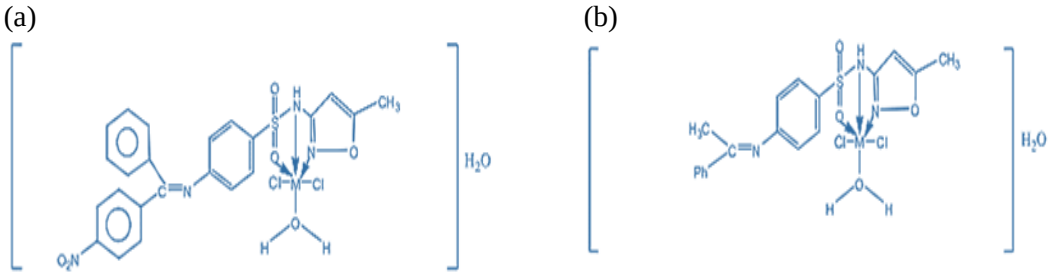
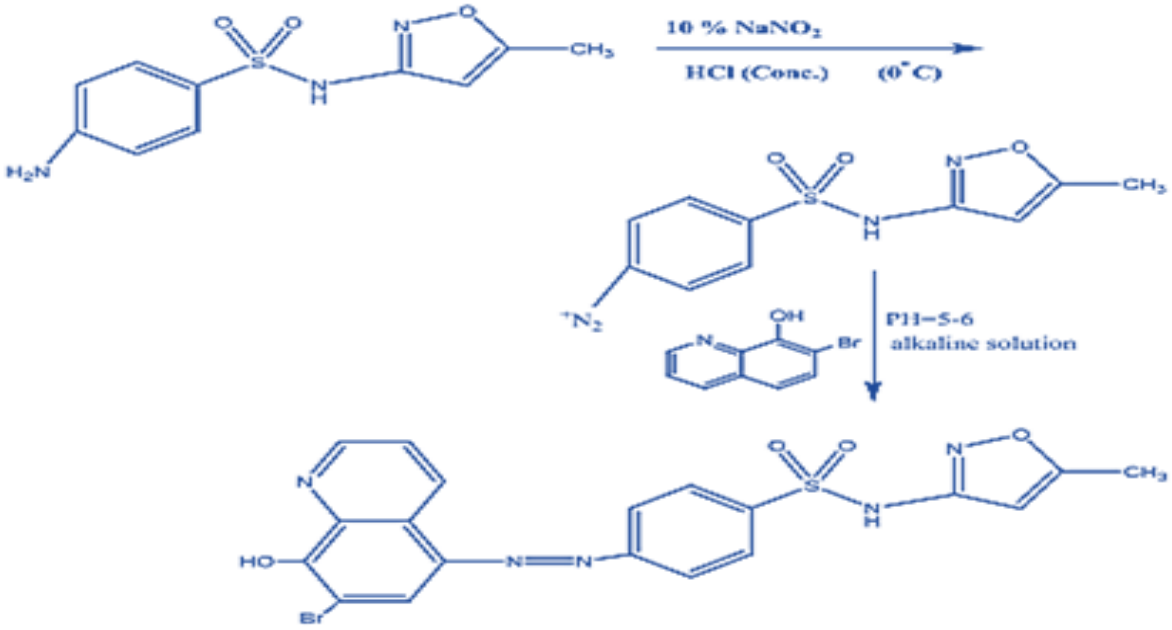


Figure 9. Chemical structures of (a) 4-nitro-benzophenone sulfamethoxazole and (b) aceto benzophenone sulfamethoxazole metal complexes. Where M= Cu(II), Mn(II) and Zn(II) (24).

3.2.4. Metal complexes of azo-sulfamethoxazole derivative

A novel azo-sulfamethoxazole derivative (HAS) (25) was synthesized through the coupling and diazotization reaction of sulfamethoxazole and 7-bromo-8-hydroxyquinoline, as illustrated in **Scheme 3**. The prepared derivative was used as a ligand to prepare metal complexes of Co(II), Ni (II), Pt (II), and Pd (II) metal ions. The ligand is coordinated to the metal ions by nitrogen and oxygen atoms as a chelating bidentate ligand with a pentagonal ring. According to the spectroscopic data, the proposed geometrical shapes of the prepared complexes were varied from a square planar for Pd(II) and Pt(II) complexes and an

octahedral shape for Ni(II) complex to a distorted octahedral conformation for Co(II) complex. High stability was exhibited by the prepared complexes when thermally analyzed, such as TGA and H_2O molecules are coordinated to the metals. Some of the prepared complexes showed a wide range of biological activities in terms of anticancer, antioxidant, and anti-inflammatory properties and high anti-fungal and antibacterial activities. Moreover, the complexes and the ligand were tested as dying agents, which showed an extensive dying property for wool fabrics. The ligand can behave differently under different pH values, which makes it a potential acid-base indicator (25).



Scheme 4. Synthesis of (HAS) ligand that derived from sulfamethoxazole (25).

3.3. Complexes of Schiff base derived from sulfonamide and isatin with Mn(II), Fe(II) and Ni (II) metal ions

A Schiff base, N-(5-Methyl-isoxazol-3-yl)-4-(2-oxo-1,2-dihydro-indol-3ylideneamino)-benzenesulfonamide, that is derived from sulfonamide and Isatin compounds were synthesized to use for preparing metal complexes of Ni(II), Fe(II), and Mn(II). The prepared ligands and complexes were characterized using various spectroscopic and physical techniques, including magnetic susceptibility, conductivity measurement, elemental analysis, and FTIR. According to the IR data, the azomethine vibrational peak of the ligand shifted to higher wave numbers after complexation, which agreed with the ligand's chelating process. The ligand coordinated with the metal ions from the azomethine's nitrogen and the ketonic moiety's oxygen, as shown in **Figure 10**. As the conductance measurement suggested, all the complexes exhibited non-electrolytic properties, and octahedral geometry was proposed for all the complexes. Antimicrobial activity was studied for the prepared complexes, which showed high responses when tested against *Mucor indicus, Aspergillus niger, Aspergillus flavus, Salmonella typhi, Escherichia coli,* and *Staphylococcus aureus* pathogenic microbes (2).

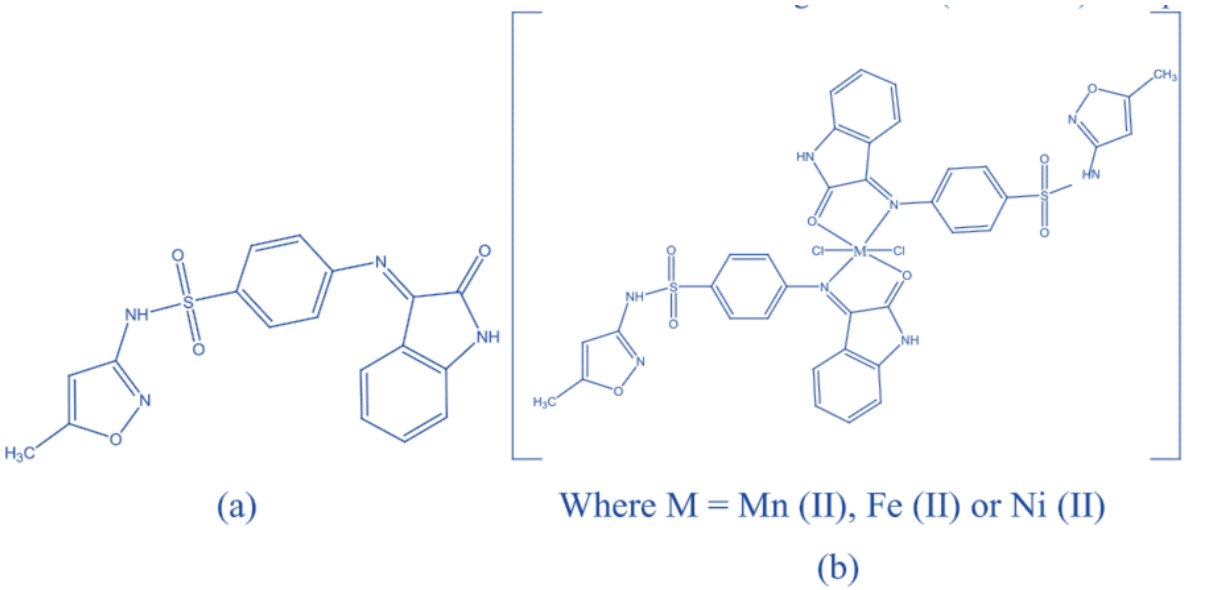


Figure 10. Chemical structure of (a) the prepared Schiff base and (b) metal complex of the Schiff base (2).

3.4. Copper(II) complex of sulfamethoxazolyl-azo-salicylic acid

The structures and biological activity of azo-sulfamethoxazole-salicylic acid (I) and its Cu complex (II) were studied, and they showed high antimicrobial properties. The Cu complex (II) toxicity is much less than the ligand (18). In silico docking, the study was conducted to theoretically investigate the binding of the compounds to DNA, which implies possessing high anti-cancer activity toward the MDA-MB-468 line of human breast cancer cells. Many features that are possessed by the prepared compounds can be advantageous materials for biomedical fields. The first crystal (I) has two polymorphic shapes in variant solvents. When it comes to the structure of the ligand and complex, an X-ray single crystal of the ligand (I) showed hydrogen bonding in forms of inter- and intra-molecular interactions, which make the 1D chain. Whereas the complex (II) structure was theoretically optimized using computational packages. When tested against the gram-negative bacteria (*E. coli*) and gram-positive bacteria (*S. aureus*), the two compounds (I) and (II) showed higher antimicrobial response when compared to sulfamethoxazole. The DFT and TD-DFT calculations were employed to obtain the spectral and electronic properties of (I) and (II) compounds. Most favorable binding sites were investigated by in-silico docking, as illustrated in **Figure 11-14**, after minimizing the drug-free energy to match the dihydropteroate synthetase site residues

(26).

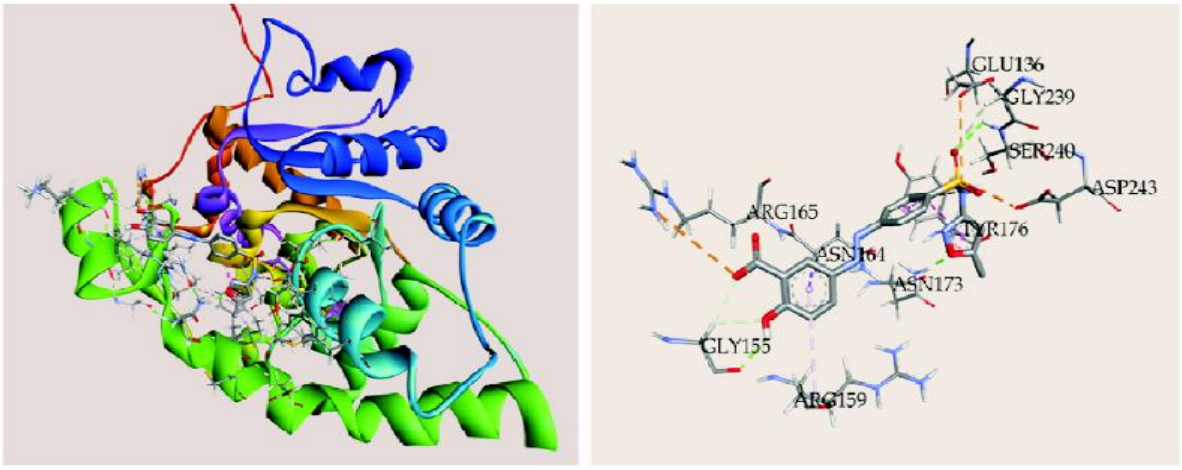


Figure 11. The mode of binding of the prepared Schiff base in the cavity of DHPS (a) 3D- and (b) 2D-interaction (26).

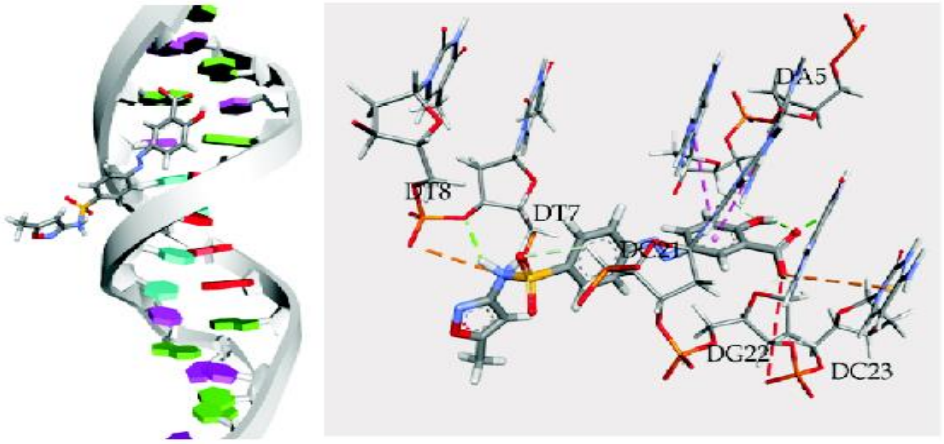


Figure 12. The mode of binding of the prepared Schiff base in the docking of DNA (26).

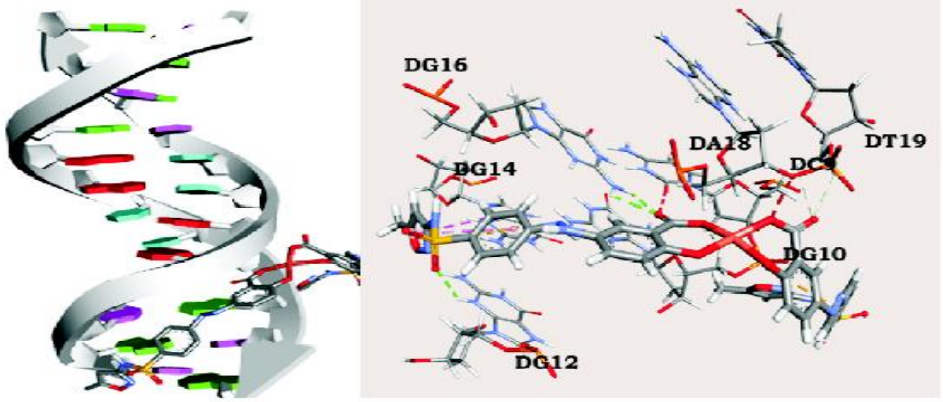


Figure 13. The mode of binding of the complex of Schiff base in the docking of DNA (26).

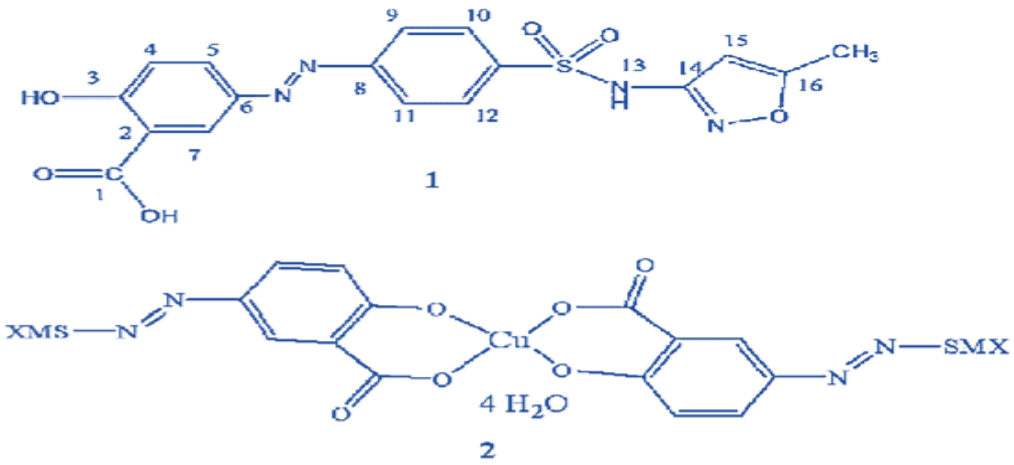


Figure 14. Chemical structure of (I) the prepared Schiff base and (II) the complex of Schiff base (26).

4. Conclusion

This literature review reports the latest and most important studies related to synthesizing organic derivatives of sulfamethoxazole and their drug-metal complexes and the biological activity associated with these complexes. These materials have high biological and pharmaceutical activities, including anti-tubercular, anti-fungal, anti-cancer, anti-bacterial, and herbicidal activities, making them very important in the pharmaceutical and medicinal industry.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Funding

There is no funding provided for this study**.**

Ethical Clearance

This work has been approved by the Scientific Committee at the University of Baghdad/ College of Education for Pure Science (Ibn Al-Haitham).

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