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Trimethoprim drug derivatives: A review of synthesis, metal complexes, nanoparticles, and biological activity

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ABSTRACT

Trimethoprim is currently often 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. We report on many Trimethoprim derivatives and their complexes were characterized using various spectroscopic techniques, including X-ray diffraction, infrared, and ultraviolet-visible measurements. In this review, the pharmacological properties and molecular mechanism of TMP in recent years are discussed. Trimethoprim derivatives are created when their molecular composition is modified, increasing the probability that they will bind to proteins. Trimethoprim is a bridging bidentate ligand that can bind to metal ions via its amino groups and pyrimidine rings. This review outlines a decade of study on the biological properties of trimethoprim derivatives. Trimethoprim derivatives have been shown to exhibit several biological characteristics throughout the last few decades. With great therapeutic results, it has been utilized to treat a wide range of diseases. Therefore, it is a promising drug with a lot of scope for study.

1. Introduction

Given their biological significance as constituents of nucleic acids, pyrimidines have garnered a great deal of attention. Pyrimidine rings can be found in several important pharmaceutical substances. Substituted 2,4-diaminopyrimidines are commonly utilized as metabolic inhibitors of the pathways that create proteins and nucleic acids while treating neoplastic and malarial disorders with chemotherapy [1]. The significance of metal ions in critical biological processes has been highlighted in numerous studies conducted recently [2–4]. The use of organic compounds in antiviral, antibacterial, and anticancer treatments has grown in popularity, demonstrating the significance of inorganic pharmacology [5,6].

Trimethoprim (TMP) (Figure 1) may bind to metal ions through potential sites. Many studies have investigated the interactions between TMP and metal ions as well as how TMP coordinates with NH_2, utilizing X-ray diffraction, infrared, and ultraviolet visible measurements [1]. Trimethoprim complexes with Ag, Zn, Cd, Hg, and Ni were described by Sekhon et al. the 4-NH_2 group on the ligand enables it to function as a monodentate, based on IR data [1]. Serval novel substituted tetrazole was produced in two steps using Schiff bases from TMP.

The initial step was to produce Schiff bases by reacting trimethoprim with ketones and aldehydes. The final step was prepared new tetrazole derivatives by reacting ready Schiff bases with sodium azide (NaN_3) in dioxin [7]. Trimethoprim is an antibiotic with a broad spectrum and antiphrastic properties [8]. Numerous *Escherichia coli* infections, including urinary tract infections, are treated with the antibiotic trimethoprim, but this drug's effectiveness is constrained by the quick spread of TMP-resistant bacteria [9].

In order to evaluate current advancements in treatment techniques, this review aims to provide a comprehensive review of TMP's biological activity. This review examines the many approaches utilized in the development and validation of TMP and its biological activity. This work further highlights the role that metal complexes and nanoparticles of TMP play in pharmacological activity.

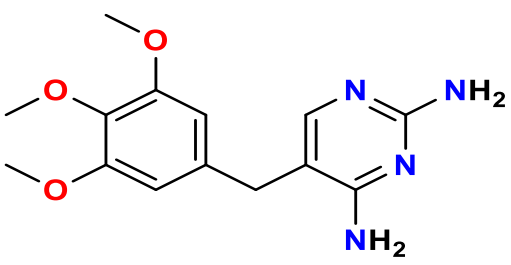

Figure 1: The structural formula of Trimethoprim drug.

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2. Methodology

A literature review was conducted to examine biological activity, metal complexes, metal nanoparticles of TMP derivatives, and evaluate the efficacy of TMP derivative treatment. We selected important research that addressed ligand, metal complex, Pyrimidine ring, and treatment parts as part of our TMP evaluation, which also involved a thorough analysis of the available data. The method to discover literature on TMP derivatives' biological effects is outlined in this section.

2.1. Selection Criteria and Procedure for Article

The search method looks for scientific data in a variety of online databases. The Cochrane Library, PubMed, Science Direct, Web of Science, Scopus, Medline, and Google Scholar were the databases that were used. The search criteria included TMP, TMP derivatives, antibacterial, and anticancer treatments. The search results were refined using Boolean operators (AND, OR, NOT) to ensure that all related studies were included. Items released between 2000 and 2024 were the only ones included in the search. Relevance to the problem was assessed based on the titles and abstracts of the identified publications. To make sure they met the inclusion requirements, the entire texts of 67 potentially pertinent papers were examined. The review included 57 articles.

2.2. Inclusion Requirements

- Peer-reviewed journal publications; studies on TMP activity; and studies outlining new and existing therapeutic approaches.

2.3. Exception criteria

- Publications older than 24 years, unless they were foundational works; studies not centered on biological activity; and non-peer-reviewed journals.

2.4. Collect of results

- A detailed summary of TMP's biological activity was produced by synthesizing the retrieved data.

3. The Trimethoprim derivatives

The rational design technique was used to examine the antibacterial properties of novel trimethoprim compounds, with the goal of improving the biological action and safety profile of TMP. New derivatives of TMP were designed, synthesized, and evaluated for their antibacterial potential. Through demethylation of TMP's trimethoxy benzyl ring, hydroxy trimethoprim (HTMP) was obtained, and structure-activity relationship (SAR) studies revealed that introducing benzyloxy and phenyl ethanone groups at the 4-position of the dimethoxy benzyl ring enhanced antibacterial activity. The results highlight the potential for designing TMP derivatives with improved antibacterial properties, which informs the current study's approach to developing novel bioactive compounds [10].

A. Al-Sahib synthesized several substituted phenol molecules, including 2-naphthol, 4-bromophenol, 2,5-dimethoxyphenol, 2,4-dinitrophenol, and 3-chlorophenol, were used to develop novel, highly effective therapeutic derivatives of TMP (Figure 2). All product chemical structures were verified using photometric techniques including FTIR and UV-visible. For these substances, the biological activities were also looked at [11].

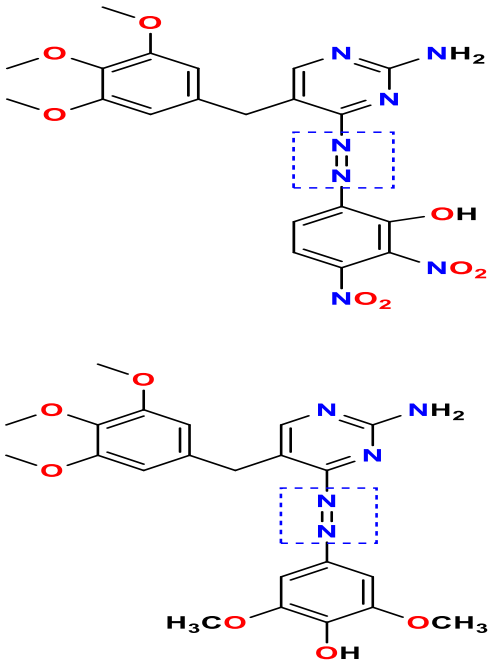


Figure 2: The novel substituted phenol molecules with TMP.

Halogen atoms can be added to drug molecules to improve their characteristics, such as enhanced hydrophobic interactions with their target and membrane permeability. To investigate how halogen substitutions affect trimethoprim's (TMP) antibacterial activity **(**Figure 3), several halogen substituted TMP were synthesized and tested against methicillin-resistant *Staphylococcus aureus* (MRSA) strains. A trend in potency that was linked with the halogen atom's capacity to promote hydrophobic contact with *S. aureus* dihydrofolate reductase (saDHFR) was revealed by the structure-activity relationship study [12].

Iodinated trimethoprim (TMP-I), the most effective derivative, exhibited resistance, however the therapeutically used TMP derivative diaveridine reduced pathogenic bacterial growth with MIC as low as 1.25 µg/mL. TMP-I and sulfamethoxazole appeared to work in concert, according to synergistic studies, just like TMP did. TMP-I's potential as a bacterial inhibitor for MRSA infections, was brought to light by the ease with which it was made from the cheap starting material vanillin [12].

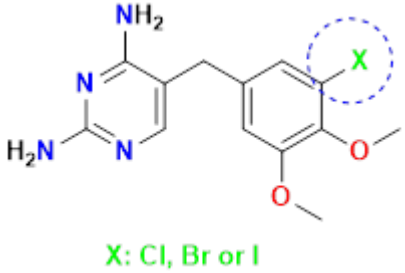


Figure 3: The halogenated TMP derivatives.

3.1 The metal complexes of TMP derivatives

Many biological systems depend on compounds with pyrimidine rings, such as trimethoprim. TMP can bind to metal ions by way of its amino groups, acting as a bridging bidentate ligand. Based on visual observations of the TMP, it has been determined by numerous researchers studying the interactions between ligands and biological metal ions that TMP is coordinated by an NH_2 nitrogen atom, and N1 of the pyrimidine ring. Seekhon et al. confirmed compounds of trimethoprim with several metal ions and found that the ligand operates as a monodentate via the 4-NH_2 group, by X-ray diffraction technique [13].

Given as metallic complexes, various drugs alter in their pharmacological and toxicological properties, new complexes of TMP have been synthesized, characterized, and studied to further our understanding of the coordination properties of TMP (Figure 4). The Zn-complex has a distorted tetrahedral geometry, while the Cd-complex centers are continually bridged by two chlorine ions to form infinite chains and a six-coordinated environment. Both structures use trimethoprim as a monodentate ligand through the pyrimidine nitrogen N(1) atom. The complexes were evaluated for their ability to combat a range of bacteria and showed activity comparable to that of trimethoprim [13].

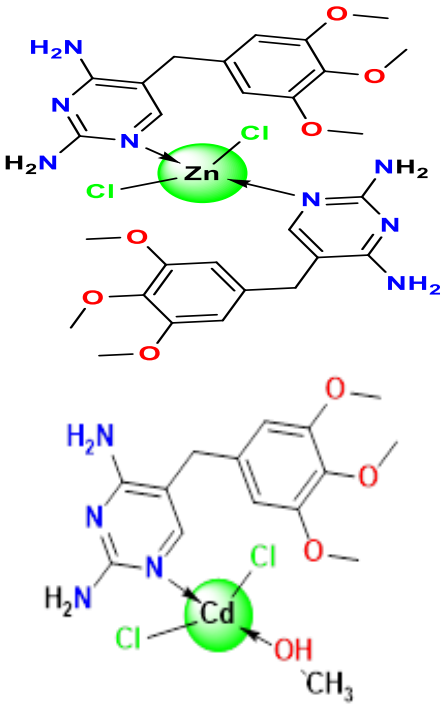


Figure 4: The $[Zn(TMP)_2\ Cl_2\ ]$ and $[Cd(TMP)Cl_2\ (CH_3OH)]$ complexes.

Four mononuclear Ag(I) complexes of trimethoprim and pyrimethamine (Figure 5) have been produced and described. Through the pyrimidine nitrogen, the trimethoprim and pyrimethamine bind to the metal ion. Since all silver complexes have more antibacterial activity than the individual drugs, prospective metal-based bactericidal agents have been found [14].

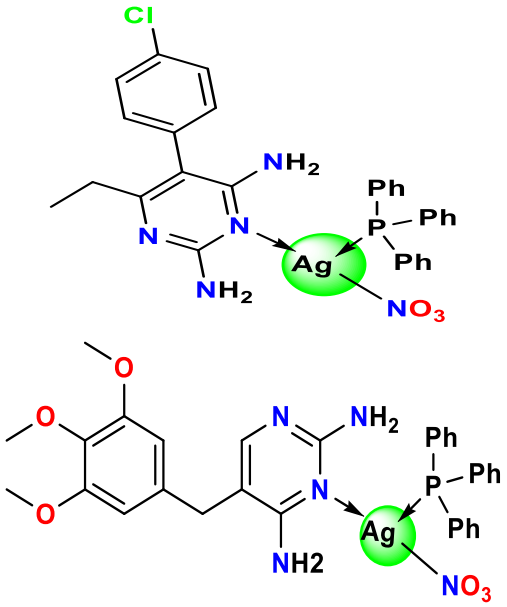


Figure 5: The $[Ag(pyrm)(NO_3)(PPh_3)]$ and $[(Ag(TMP)(NO_3)(PPh_3)]$ complexes.

Trimethoprim produces new ligands with Fe^{+3} and Cu^{+2} complexes (Figure 6). To produce novel ligands, add trimethoprim to gallic chloride in a nucleophilic manner, then to ammonium thiocyanate and gallic chloride solutions in a nucleophilic manner. Spectroscopy confirmed and produced the complexes in a 1:2 molar ratio. The ligands interact with ferric and copper ions via phenolic oxygen and NHC=O's nitrogen atoms, serving as many sites as possible. The synthesized compounds exhibited more inhibitory efficiency than TMP [15].

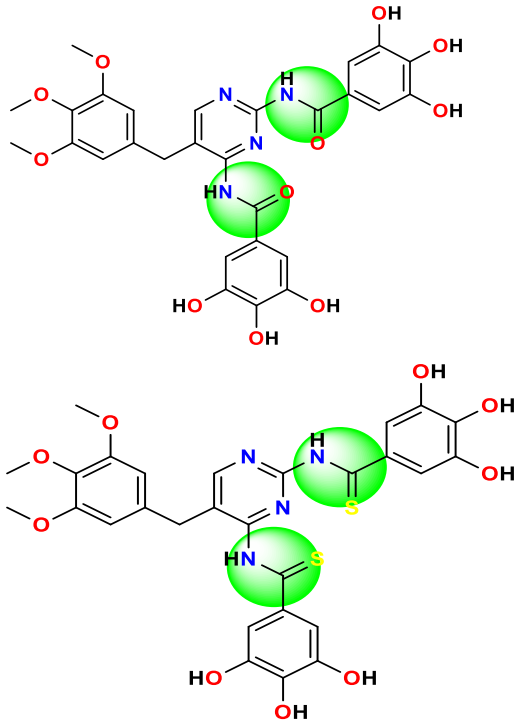


Figure 6: The new ligands derived from trimethoprim with gallic acid.

Another new complexes were prepared by reaction of new ligand (trimethoprim with 2- hydroxy-naphthaldehyde), with the metal ions in ratio (1M: 2L) and were confirmed various by spectral analyses (Figure 7). All complexes show octahedral structures except Pd complex is square planar structure. The derivatives demonstrated effective antifungal and antibacterial properties [16].

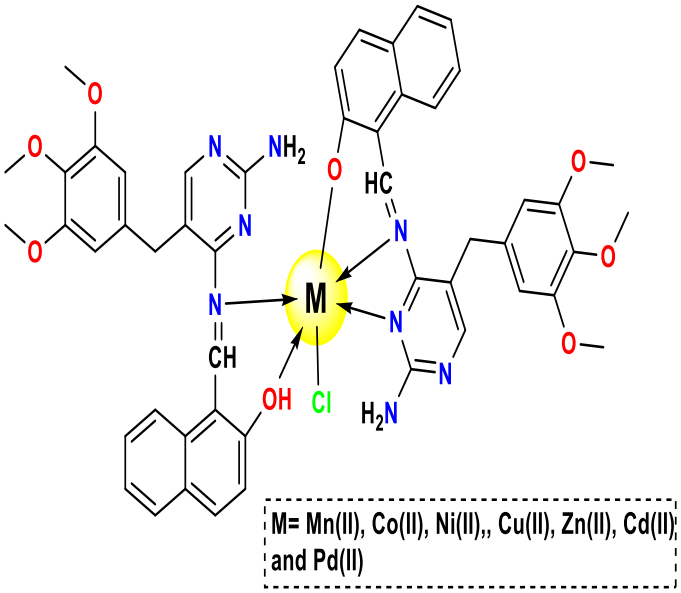


Figure 7: The complexes from trimethoprim with 2-hydroxy-naphthaldehyde.

TMP's high adsorption selectivity for heteroatoms like N and O make it highly effective in inhibiting steel corrosion in various situations. Trimethoprim adheres to carbon steel surfaces by interacting with heteroatom lone electron pairs and metal atom d-orbitals [17–19]. Because organic chemicals decompose down with temperature and time, inorganic inhibitors are used [20], then the TMP complexes that are employed as inhibitors [21]. Nicotinamide and trimethoprim produced complexes with metal ions (Figure 8), which inhibited *Escherichia coli* and other species more effectively than their original ligands [22].

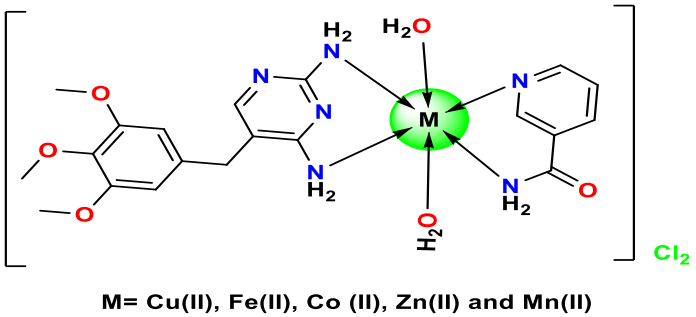


Figure 8: Proposed Structure of $[M(NIC)(TMP)(H_2O)_2].Cl_2$.

4. Metallic Nanoparticles Functionalized with TMPs

Applications for metallic nanoparticles in biology are numerous [23,24]. Silver-containing antibacterial nanoparticles can also aid in lowering side effects and drug dosage requirements. Drug effectiveness is increased when nanostructures are added [25–27].

Because of their special qualities and potential applications in delivery of drugs, therapy, and imaging, nanoparticles have garnered a lot of attention in the field of biological research. To assess and improve the efficacy of sulfamethoxazole and TMP, new nanoparticles were produced. The morphologies of Fe_3O_4/Ag and Fe_3O_4@SiO_2/Ag were found to be sphere-like, with average diameters of 33.2 and 35.1 nm. Trimethoprim and sulfamethoxazole alone showed zeta potentials that increased to zero or even greater positive values when conjugated with the NPs, from -30.6 and -10.0 mV, respectively. The release kinetics investigation showed that 64.7% of the drugs were freed from the carriers in less than 40 days. The results imply that administering antibiotics in conjunction with these NPs can lower dosages and side effects [28].

Using voltametric techniques and a carbon paste electrode modified with sodium dodecyl sulphate (SDS), an anionic surfactant, and nanostructured zinc oxide nanoparticles (ZnO/CPE), TMP was identified. TMP's electrochemical properties were investigated in a 0.2 M pH 3.0 phosphate-buffer solution. The developed electrode had the highest peak current in comparison to the developing CPE. Several different parameter variations were examined. By using the irreversible electrode process of TMP, two transferred electrons were used to control diffusion. The lowest limit of detection was found to be $2.58x\ 10^{-8}$ M. By adjusting the concentration, the effective concentration range ($8.0x\ 10^{-7}$-$1.0\ x\ 10^{-5}$ M) of TMP was obtained. With remarkable recovery data, this technique effectively identified TMP in pharmaceutical dosages and urine samples, proving the usefulness of the produced electrode in clinical and pharmaceutical sample analysis [29].

A novel electrochemical sensor that simultaneously detected TMP and sulfonamides (SMX) was built on graphene (GR) and ZnO nanorods (GR-ZnO/GCE). The SEM image demonstrated that the morphology of ZnO was rod-shaped. ZnO nanorods are in the hexagonal wurtzite phase, based on the XRD data. The electrochemical experiment results showed that the developed sensor exhibited exceptional electrocatalytic performance toward theoxidation of SMX and TMP due to the synergistic interaction between GR and ZnO.

The DPV approach was used to find SMX and TMP at 0.85 and 1.06 V. With limit of detection (LOD) of 0.4 and 0.3 µmol/L for SMX and 1-180 µmol/L for TMP, the GR-ZnO/GCE demonstrated superior wide linear responses under ideal circumstances. The selectivity, stability, repeatability, and anti-jamming of the sensor are all good. We assessed the recovery rates of SMX and TMP in lake water, tap water, urine, and serum, ranging from 93.2% to 108%. The proposed sensor shows promise for applications in environmental protection and biomedicine [30].

5. The Structure Activity Relationship of TMP Derivatives

The SAR study of TMP derivatives indicates how structural modifications influence their antibacterial efficacy and binding affinity to DHFR. The modifications have significant effects on performance as the 2,4-diaminopyrimidine moiety makes hydrogen bonds with key residues such as Asp27, Ile5, and Phe92, which have significance for DHFR reduction. Substituting benzyloxy or phenylethanone groups for the 4-methoxy group improves interactions within the DHFR binding site and increases activity. This replacement demonstrated strong antibacterial effectiveness, with MICs of 4 µM against *E. coli* and 5 µM against *S. aureus*. Higher log P values indicate that hydrophobic derivatives are more efficient against Gram-negative bacteria, perhaps due to better penetration of their lipophilic outer membranes. Replacing the 4-amino group of the pyrimidine ring in Schiff base derivatives resulted in poor or no antibacterial action, indicating the need to maintain the 4-NH_2 group [10].

Agnieszka Wróbel et al. synthesized and studied TMP analogs with amide bonds. Adding amide bonds, halogen or methoxy groups, and double bonds improves the binding ability of TMP derivatives to DHFR and DNA, according to SAR study. The changes enhance DNA binding and inhibitory activity, with key interactions occurring at residues such as Phe-34 and Glu-30. Molecular docking studies indicate that these analogs have strong hydrogen bonding and π-π stacking interactions, making them promising candidates for antibacterial and anticancer therapy [31].

The SAR investigations of TMP derivatives are impacted by the structure of TMP, which includes the amino groups, methoxy groups, and pyrimidine ring. Metal ions are coordinated with biological targets by functional groups, which increases the biological activity of derivatives. The pyrimidine nitrogen atoms and amino groups of TMP act as bidentate ligand, were enabled to form stable complexes with metals. The bioactivity of complexes is affected with varying coordination geometries for example, octahedral for Fe(III) and square-planar for others. The Au complexes have strong anticancer activity against *HepG2* and *HCT-116* cells, with low IC_{50} values [32].

Ag(I) complexes have more antibacterial activity than TMP. By changing the electronic distribution of methoxy groups or pyrimidine rings, the derivative's stability, solubility, and bioavailability can be improved. Because it influences solubility and cellular absorption, the ratio of hydrophilicity to lipophilicity is important in biological systems. The chemical structure and modifications of TMP derivatives influence their therapeutic properties [32].

6. The main biological properties of TMP derivatives

TMP derivatives have a broad range of biological actions, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic effects [33]. TMP was frequently combined with sulfamethoxazole, a sulfonamide antibiotic that produces an *in vitro* synergistic antibacterial action, at a 1:5 ratio. This combination is also referred to as co-trimoxazole [34]. Additionally, when both drugs are used together, resistance to either one develops less frequently [35]. The binding sites in TMP such as for the carbonyl, amino groups make it a Schiff base.

TMP is readily absorbed, reaching peak plasma concentrations in 1- 4 hours. Some derivatives may be developed to increase solubility and bioavailability, resulting in more effective absorption. TMP is widely distributed throughout the body, including bronchial secretions, vaginal fluids, and placental tissues, and is approximately 44% protein bound in plasma. Metabolism occurs predominantly in the liver via enzymes such as CYP3A4, however TMP is a minor inhibitor of CYP2C8, influencing the metabolism of co-administered drugs. Approximately 46-67% of TMP is eliminated unaltered in urine by glomerular filtration and tubular secretion. Chemical modifications of TMP derivatives may improve stability, extend half-life, and optimize renal clearance. Furthermore, when used with other drugs, such as metformin, TMP and its derivatives interact with transporters like MATE1 and OCT1, affecting their pharmacokinetics and requiring dose modifications [36].

Using a Betti type reaction, Pavithra et al. synthesized a series of 1,1- ((5-(3,4,5triethoxybenzyl)-pyrimidine-2,4-diyl)) bis(azanediyl)) bis(substituted phenyl methylene)) bis(naphthalen-2-ol)) and assessed their pharmacological features, such as antibacterial and antioxidant properties using the DPPH and Agar diffusion methods. All the derivatives were investigated using FT-IR, ^{1}H and ^{13}C NMR, and mass spectrum analysis.

The structural characteristics of derivatives and electron-donating groups are responsible for these activities. Molecular docking demonstrated significant receptor-ligand interactions (binding energies ranging from -4.1 to -7.3 kcal/mol), and molecular dynamics simulations confirmed the stability of the protein-ligand complexes. These computational investigations further established their pharmacological relevance. According to these results, the derivatives may be useful as antioxidant and antibacterial therapeutic potential [37].

6.1. Anti-bacterial activity of Trimethoprim derivatives

A well-known antibiotic in the dihydrofolate reductase inhibitor class of drugs is trimethoprim. By preventing the synthesis of tetrahydrofolic acid, an essential component for the creation of bacterial DNA, RNA, and proteins, it is mostly used to treat bacterial infections. Trimethoprim has a bacteriostatic action via interfering with the folate pathway by inhibiting the enzyme dihydrofolate reductase. In clinical settings, trimethoprim-sulfamethoxazole (TMP-SMX or co-trimoxazole) is a commonly used medication combination that is used in conjunction with sulfamethoxazole, a sulfonamide antibiotic, to increase its efficacy. This combination is a mainstay in the treatment of lung infections, urinary tract infections, and some forms of diarrhea because it is especially efficient against a wide range of Gram-positive and Gram-negative bacteria. Trimethoprim is widely used, but resistance to it has

developed. This has led to the development of new derivatives and combination therapies to overcome the resistance of bacteria and broaden the drug's therapeutic uses. Because of the pyrimidine ring's nitrogen atoms function well as a chelating agent for metal ions [38–41].

TMP derivatives enhance the pharmacodynamics of TMP by suppressing DHFR and addressing bacterial resistance. The compounds enhance treatment efficacy by targeting DHFR, an enzyme involved in bacterial DNA and protein synthesis. Structural modifications, including amide bonds and methylene bridges, improve binding to DHFR's active site and maintain interactions with key residues like Glu-30 and Phe-34. Certain derivatives are more effective than TMP (IC_{50} = 55.26 µM) due to increased binding affinity. TMP derivatives bind to DNA in AT-rich regions and inhibit DHFR, increasing antibacterial activity and create new therapeutic pathways [42].

Umer Rashid et al. prepared 19 new trimethoprim derivatives (Scheme 1 and Figure 9) and evaluated for their antibacterial potential. The synthesized derivatives were excellent antibacterial activity against strains of *S. aureus* and *E. coli* with higher inhibition effectiveness than Trimethoprim. To investigate the various types of interactions and binding orientations, were docked using the Genetic Optimization for Ligand Docking (GOLD) suit v5.4.1. The compound TMP derivative (4b) has the highest GOLD docking score of 79.89 and exhibits four conventional hydrogen bonds with Ile5 (1.84 Å), Asp27 (1.49 Å), and Phe92 (2.99 Å) (**Figure 10**). A comparative docking analysis based on TMP's mechanism of action, with DHFR as the target, successfully explained and rationalized the *in vitro* data and the antibacterial activity. Thus, docking studies and *in vitro* tests proved that the pharmaceutical design was successful [10].

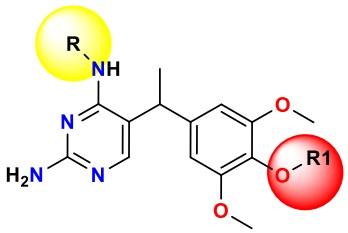


Figure 9: The general structure of novel TMP derivatives for example (4b), R=H and R1= -CH_2-(4-OCH_3-C_6H_4).

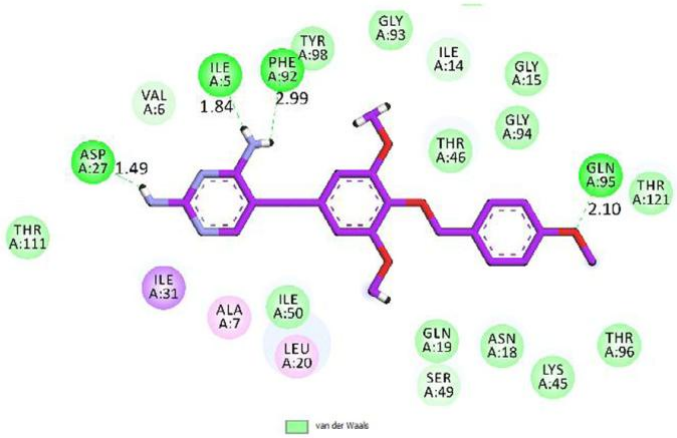
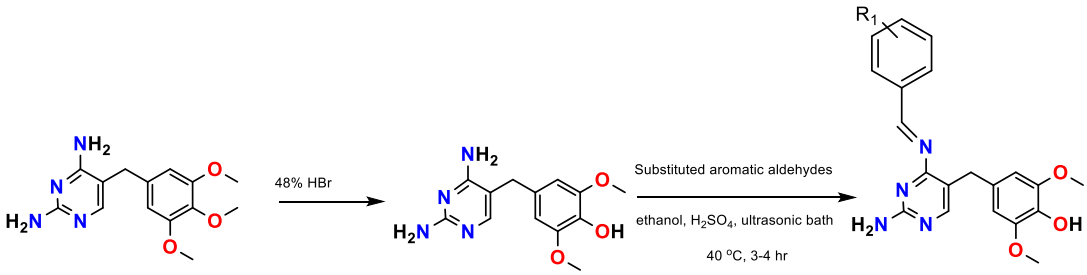


Figure 10: 2D binding interaction plot of the compound TMP derivative(4b).



Scheme 1: Synthesis of new derivatives from TMP.

Recently, there has been a lot of interest in metal complexes because of their stability and versatility, and remarkable biological qualities [38,43,44]. The trimethoprim and cyclohexanone complexes (Figure 11) demonstrated antibacterial action against pathogenic microbes. Antimicrobial activity data showed the following pattern: Schiff base > metal complexes > TMP [45].

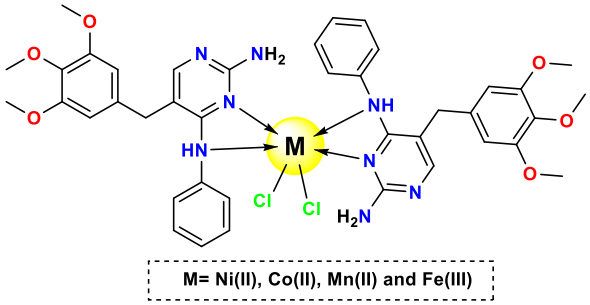


Figure 11: The metal complexes derived from trimethoprim with cyclohexanone.

A novel derivative of Trimethoprim containing o-hydroxybenzaldehyde and its metal complexes was produced using zinc and manganese salts (Figure 12) and described using various techniques. The azo methine, phenolic oxygen, and imine nitrogen atoms form a tridentate ligand that coordinates with metal ions. The derivative and complexes showed higher antibacterial activity compared to trimethoprim [46].

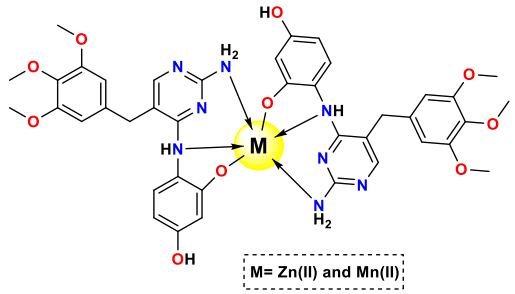


Figure 12: The Zn and Mn Complexes from trimethoprim.

Previous studies have demonstrated the synthesis of novel ligands derived from trimethoprim and their corresponding Iron(III) and Copper(II) complexes. Specifically, ligands were synthesized via nucleophilic addition of trimethoprim to Gallic chloride. The ligands acted as multidentate chelators, coordinating with the metal ions via the nitrogen atoms of the NHC=O group and phenolic oxygen atoms. *In vitro* tests revealed that the ligands and their metal complexes displayed significant growth inhibitory activity against Gram-negative *Salmonella spp.* and Gram-positive *Staphylococcus spp.*, with higher inhibition effectiveness than Trimethoprim. This underscores the potential of these metal-ligand systems as promising candidates for antimicrobial applications [15].

6.2. Anti-cancer activity of Trimethoprim derivatives

Cancer is the second greatest cause of mortality worldwide and a serious public health concern. The 2020 coronavirus (COVID19) pandemic caused a delay in cancer diagnosis and treatment, which raised mortality [47–51]. Therefore, the creation of new drugs for cancer treatment is always essential. We looked for several compounds that could be developed into new anticancer drugs, but we were especially interested in trimethoprim derivatives because they had a strong therapeutic effect against cancer.

TMP derivatives inhibit DHFR, a key enzyme in folate metabolism responsible for DNA synthesis and cellular reproduction. This inhibitor blocks the synthesis of tetrahydrofolic acid, which is particularly damaging in rapidly proliferating cells like cancer cells. Trimethoprim derivatives have enhanced affinity and selectivity for human DHFR, making them promising anticancer drugs [41,52].

TMP derivatives, when reacted and attached with metals, have significantly enhanced pharmacodynamic properties and are potent anticancer drugs. Their anticancer effects are explained by these complexes' ability to disrupt essential cellular processes including transcription, DNA replication, and cellular metabolism. Through the addition of structural and electrical modifications, metal coordination with TMP enhances its binding selectivity and affinity for cancer cell targets. In the process, cytotoxic effects are increased and the possibility of adverse effects on healthy cells is decreased. Specifically, the TMP-Ti complex, with an IC_{50} of 29.46 µM, is the most effective derivative against *HeLa cervical* cancer cells. It is believed to be helpful in disrupting cellular metabolism due to its ability to initiate cytotoxic pathways, change mitochondrial function, or generate reactive oxygen species (ROS). TMP-Cu showed low anticancer activity against *PC3* prostate cancer cells (IC_{50} = 31.95 µM), suggesting that it is adaptable to different forms of cancer [53].

The pharmacodynamics of these TMP-metal complexes are further enhanced by the interactions of TMP derivatives with DNA, where they bind to small grooves and block transcription and replication. These mechanisms are present in other TMP-metal complexes that have strong DNA binding and cytotoxic effects, such TMP-Au and TMP-Pt. TMP-Au (~10 nm) whose nanoscale size enhances its anticancer effectiveness through promoting higher tumor penetration and cellular absorption [53].

The formazan was combined chemically with trimethoprim to improve its efficacy in treating malignant tumors and reducing their size. This led to a greater increase in the manufactured derivative's importance than the original drug, as seen in Figure 13. Initial reactions of trimethoprim with hydrazine resulted in hydrazo-trimethoprim, which was further reacted with several aldehydes to make imine- trimethoprim, and lastly with diazonium salt to yield trimethoprim drug- formazan compounds. Spectroscopic techniques were used to study any drug derivatives in order to optimize chemical structures for active groups and habitats, as well as the biomechanical test (MTT) against breast cancer cells [54].

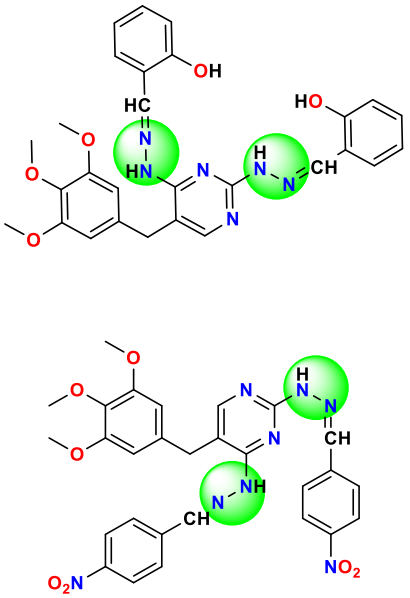


Figure 13: Trimethoprim-Formazan derivatives.

Sulfazan derivatives (Figure 14) are considered an advanced form of organic chemical compound by Nagham Aljamali, who also studied the compounds' stability and fastness properties and set the conditions for their production and properties [55]. These compounds were also improved in their structures through spectral methods [55,56]. Its effectiveness and efficiency against breast cancers have been thoroughly investigated. In order to assess the effectiveness of the two derivatives, sulfazan and formazan, we employed two different cell types: healthy and infected [55].

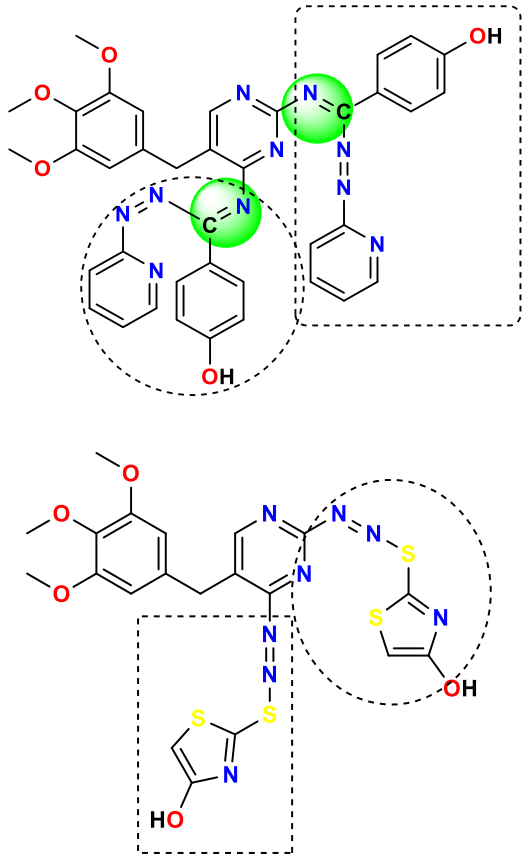


Figure 14: Formazan-Trimethoprim and Sulfazan-Trimethoprim drugs.

TMP drug complexes were created and analyzed using several spectroscopy techniques. The iron(III) complex has an octahedral structure, while the others have a four-coordinate geometry (Figure 15). TEM and XRD investigations indicate that the Au complex has a nanoscale of around 10 nm. The Au complex's cytotoxicity was tested against colon cancer (HCT-116) and hepatocellular carcinoma (HepG2) cell lines. The Au complex had IC_{50} values of 7.46 µg/mL for HepG2 and 9.30 µg/mL for HCT-116 cancer cell lines [32].

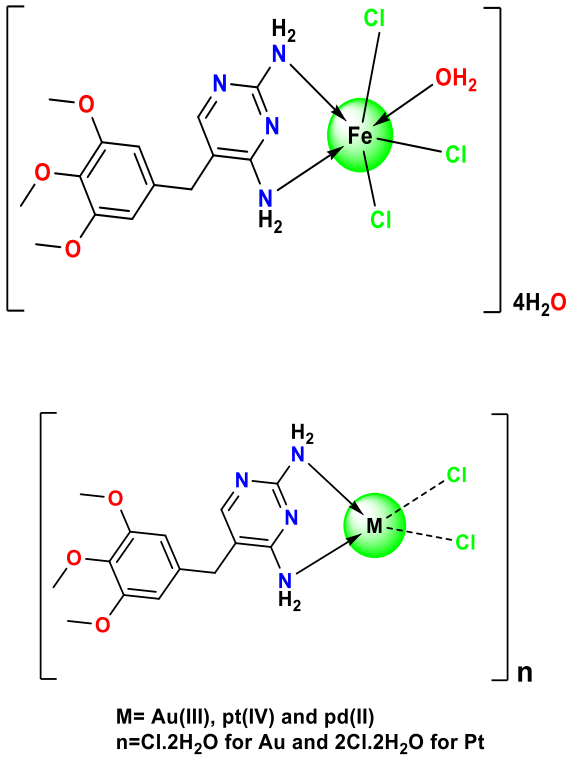


Figure 15: Different complexes from TMP with Au(III), Pt(IV) and Pd(II) ions.

TMP analogs with amide bonds (O=C-NH) have been created in a new series (Scheme 2 and Figure 16). Molecular docking was used to establish their ability to bind the dihydrofolate reductase enzyme and a dihydrofolate reductase (DHFR) inhibition study. Ethidium displacement test results demonstrated their ability to bind DNA. Utilizing DNA from the calf thymus, T4 coliphage, poly $(dA\text{-}dT)_2$ and poly $(dG\text{-}dC)_2$, tests were conducted to validate the potential for DNA to bind in a minor groove and to identify the connection constants. The molecular docking tests show that TMP analogs have a higher affinity for the human DHFR (PDB: 1U72) when an amide bond is added [42].

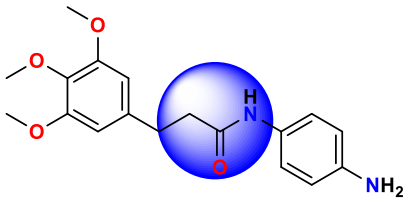
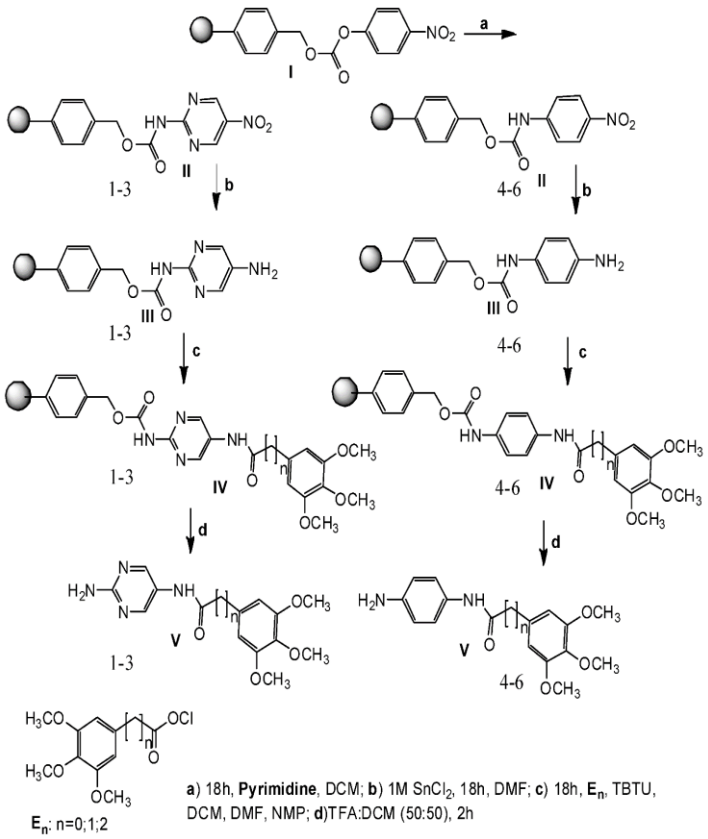


Figure 16: Trimethoprim analog containing amide bond.



Scheme 2: The synthetic pathways of TMP derivatives containing amide bond.

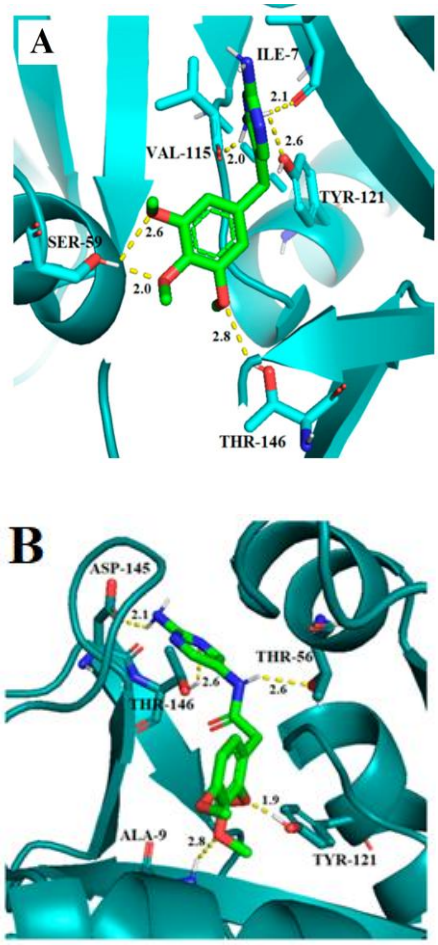


Figure 17: The binding modes of (A) TMP, and (B) TMP derivative in the active site of human DHFR.

The results showed that TMP analogs had similar binding affinities, ranging from -7.7 to -8.3 kcal/mol. TMP ligands interact with receptors through methoxy groups, amine and peptide groups, and aromatic rings. The compound N-(2-aminopyrimidin-5-yl)-2-(3,4,5-trimethoxyphenyl) acetamide, has the lowest binding energy, scoring -8.3. It forms five hydrogen bonds with the following residues: Tyr-121 (O-H···O, 1.9 Å), Asp-145 (N-H···O, 2.1 Å), Thr-146 (O-H···N, 2.6 Å), and Ala-9 (N-H····O, 2.8 Å). All the analogues showed promising antibacterial properties with binding energies that were only about 1.2 kcal/mol lower than the well-known DHFR inhibitor MTX (Figure 17). Moreover, *in vitro* studies on cancer cell lines are required to evaluate their effectiveness and possible therapeutic uses [42].

In a study of C7-TMP derivatives targeting a specific pocket in C. hominis (ChDHFR), seven-ethyl TMP outperformed TMP by fourfold (Scheme 3 and Figure 18).

In order to determine if interactions with Cys 113 increase the efficacy of smaller molecular weight compounds, we docked TMP analogs with C7 modifications. Following its contact with Cys 113, 7-Ethyl TMP extended the phenyl group into two distinct hydrophobic pockets. The interactions between the substituted phenyl group and those pockets are shown in Figure 19. The most powerful TMP was anticipated to be 7-Ethyl TMP, whose binding energy was -58.46 kJ/mol. The energies of 7-methyl TMP and 7-isopropyl TMP were -56.85 and -56.98, respectively, in comparison. The development and assessment of C7-TMP analogs resulted in a four-fold increase in effectiveness [57].

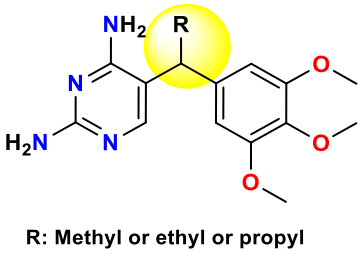


Figure 18: C7-substituted analogs of trimethoprim.

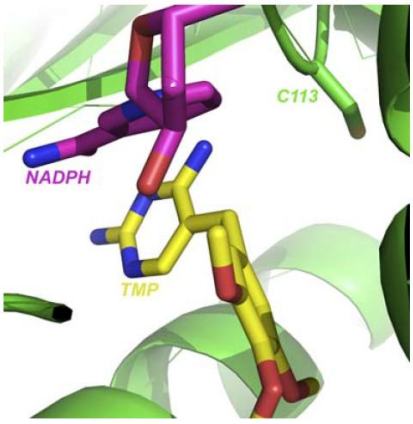
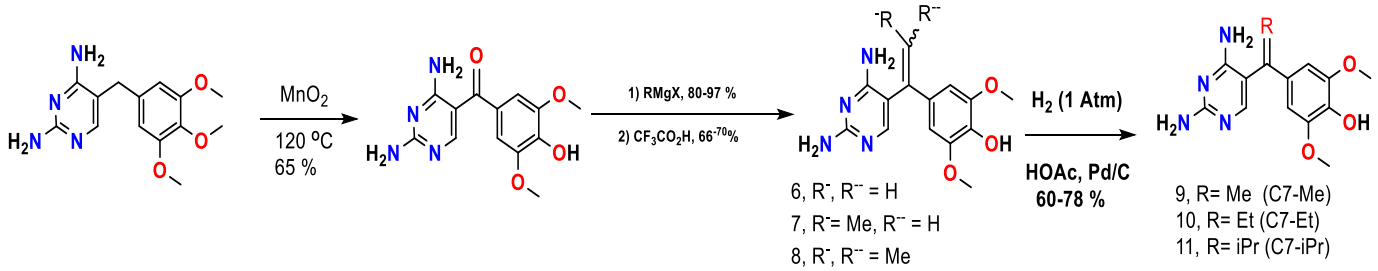


Figure 19: 3D of 7-Ethyl TMP interacted with Cys 113.



Scheme 3: Synthesis of C7-substituted analogs of trimethoprim.

Conclusion

Here, the review gives brief details about the structure, derivatives, metal ions with trimethoprim, metal nanoparticles, and biological activity such antibacterial, and anticancer of TMP derivatives. Due to TMP containing pyrimidine ring, amino and methoxy groups, which act as a bridging bidentate ligand, with the ability to bind to metal ions, and become a strong antibacterial, and anticancer capability, which is responsible for most of its actions. Generally, the increase in the numbers of receptors for TMP derivatives is caused by changing their molecular composition, which increases their chances of binding with proteins and improves their pharmacodynamics properties. They were discovered to be a more powerful DHFR inhibitor with significantly higher in vitro efficacy. Regular use of TMP has been shown to significantly decrease the risk of oxidative stress-related disorders, such as cancers. It is vital to confirm that TMP is a drug that requires further study.

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List of Abbreviations

^{1}H-NMR	Proton nuclear magnetic resonance
DHFR	Dihydrofolate reductase
DPPH	The 2,2-Diphenyl-1-picrylhydrazyl
FR-IR	Fourier-transform infrared spectroscopy
GOLD	The Genetic Optimization for Ligand Docking
GR-ZnO/GCE	Graphene /ZnO nanorods
HepG2	Hepatocellular carcinoma
K_m	Kinetic characterization of dihydrofolate reductase
LOD	Limit of detection
MATE1	Multidrug and toxin extrusion protein 1
MRSA	Staphylococcus aureus strains
MTT	Colorimetric assay for assessing cell metabolic activity.
OCT1	Organic cation transporter 1
PC3	Human prostate cancer cell line used in prostate cancer
PDB	Protein Data Bank
ROS	Reactive oxygen species
SAR	The structure of activity relationship
SMX	Sulfamethoxazole
TMP	Trimethoprim
UV–visible	Ultraviolet–visible spectroscopy