

Review Article

Microbial activity of some heterocyclic Schiff bases and metal complexes: A review

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Abstract

Microbial resistance to current drugs associated with food spoilage and complications in diseases' treatment have resulted in increased mortality rate globally. Schiff bases are an important versatile class of organic compounds with notable pharmacological properties for various industrial applications. They are usually synthesized from a condensation reaction between a primary amine and a carbonyl. They have a wide range of activities against microbes and demonstrate good antimicrobial activity against fungi, bacteria, parasites, and viruses. The antimicrobial activity of Schiff base ligands is usually better upon metal complexation as a result of their chelating behaviour. The synthesis of Schiff bases and their metal complexes are well-documented. Therefore, it is important to categorize and compile them according to their biological significance. In this review, the antibacterial, antifungal, antiparasitic and antiviral activity of some selected heterocyclic Schiff bases and their metal complexes are discussed.

Keywords: Heterocyclic Schiff bases, Metal complexes, Antibacterial, Antifungal, Antiparasitic, Antiviral

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INTRODUCTION

Schiff bases - definition and concepts

Schiff bases are compounds containing carbon-nitrogen double bond generally known as azomethine or imine linkage. They were named after their discovery in 1864 by an Italian naturalized chemist, Hugo Joseph Schiff [1]. They are structure-based compounds in which the oxygen atom of the carbonyl group (C=O) of an aldehyde or ketone is replaced by the nitrogen of primary amine [2]. Knowledge of Schiff bases dates as far back as 1864 when the Hugo Schiff reported the successful formation of

an imine linkage for the first time [3]. Schiff bases form a class of important organic compounds and represent the most utilized group of organic molecules. Compounds containing double bond carbon-nitrogen functional group in their molecules have contributed significantly to progress in science, especially medicinal chemistry. They are useful in day-to-day life because of the unlimited potency of the azomethine group and ease in their formation.

Synthesis of Schiff bases

Schiff bases are generally formed as a result of the chemical reaction between a primary amine

(R-NH₂) and a carbonyl group (aldehyde: R-CH=O or ketone R₁R₂C=O) in the presence of chemical catalysts and under constant heat [4]. The chemical equation is presented in Figure 1.

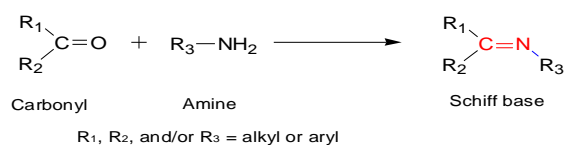


Figure 1: General procedure for Schiff bases formation

Compounds containing azomethine functional groups could be obtained from various natural and non-natural sources; they can also be synthesized in the laboratory. Several methods have been applied to synthesize Schiff bases. Organic methods, commonly known as the classical method usually take place in alcoholic conditions. This is usually followed by the removal of solvents, mainly in the case of aprotic dipolar solvent with a high boiling point [5]. Other synthetic methods do not involve the use of chemical solvents. Microwave-assisted methods have been used to synthesize Schiff base ligands [6-9] and are documented as green synthesis. Bhagat *et al* [10] and Salve *et al* [11] have successfully synthesized Schiff base compounds using water as a solvent. The mechanism of Schiff base formation involves a nucleophilic attack by the amine on the electrophile site with the formation of a tetrahedral intermediate. This process, therefore, leads to the liberation of water and the formation of imine group irrespective of the routes or methods adopted (Figure 2).

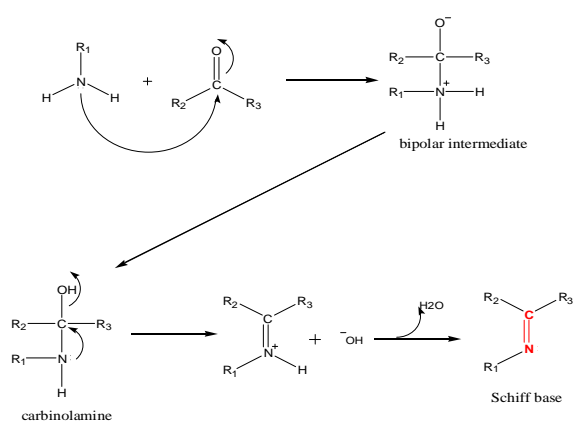


Figure 2: Mechanism of Schiff bases synthesis

Biological applications of Schiff bases

Over the past decades, interest in Schiff bases has increased significantly as demand for new compound formulations with desired functionalities rises. Schiff bases possess

excellent characteristics due to the carbon-nitrogen double bond in their structure. The beneficial properties of Schiff base compounds are not limited to the azomethine bond, but are structurally enhanced by numerous scaffolds, such as aromatic and substituted aromatic compounds. Besides, the presence of electron-rich species such as nitrogen (N), oxygen (O), sulfur (S) in the Schiff base molecule are reported to greatly increased their applications [12,13]. For instance, Schiff bases derived from salicylaldehyde derivatives with -OH group in *ortho* and *para* positions are of interest mainly due to the existence of O-H...N and O...H-N type hydrogen bonds, which undergo excited state tautomerization between enol-imine and ketoenamine [14]. In addition, the presence of nucleophile groups is very important in chelating metal ions, which have found intensive applications in drug discovery, catalysis and chromatography applications [15].

Schiff bases are structurally diversified and very useful in the scientific body. The imine properties of Schiff bases have gained the attention of many scientists worldwide due to their multiple facet applications. They are used as dyes, chelating agents, antimicrobial agents, and as a prototype for antibiotics development [16-18]. Imines Schiff bases have been publicized as good antibacterial, antifungal, antiviral, anti-inflammatory, antimalarial, and antioxidants agents [19-22]. They owe their multifunctional properties to countless aldehydes/ketones and amines used in condensation reactions, including mainly, but not limited to, aromatic and heterocyclic rings.

Heterocyclic Schiff bases

In the development of novel compounds with biologically active properties, Schiff bases derived from heterocyclic rings present many advantages. The common heteroatoms found are usually nitrogen, oxygen, and sulfur (NOS). Among the various types of heterocycle molecules studied [23,24], nitrogen (N) contained compounds such as benzimidazole and its derivatives represent groups of important chromophores with desirable biological properties [25,26]. Benzimidazole is a bicyclic carbon and nitrogen-containing heterocycles with a broad spectrum of pharmacological activity [27]. Benzimidazole nuclei are very important pharmacophores with increasing attention in modern drug discovery [28]. Literature shows that many human pathogens and microbial agents are very sensitive to Schiff bases with benzimidazole moiety. These include bacteria [29,30], fungi [31], and viruses [32,33], which are

discussed subsequently in this review. Moreover, benzimidazole Schiff bases have also been reported to have antioxidant, anti-inflammatory, analgesic, antitumor, anticancer, and inhibitory properties [34-39].

Antibacterial activity

Bacteria threatening life and affecting the health status of people living in South Africa and regions beyond include both Gram-negative and Gram-positive bacteria. The uptake or the ingestion of water and/or food contaminated with bacteria such as *Salmonella typhi*, *Escherichia coli* including *Clostridium*, *Pseudomonas* and *Bacillus* species can affect human and animal health causing diseases such as typhoid, fever, and diarrhoea [40-42]. Therapeutic measurements to address these infections witness many drawbacks due to microbial resistance [43]. Schiff bases are considered good antibacterial agents and their biological activities have been enhanced by metal complexations as clearly documented in the literature with bacteria responding differently.

Shanty *et al* [44] synthesized seven different heterocyclic Schiff bases and investigated their antibacterial activity. Accordingly, the Schiff base ligands were obtained by reacting carbonyls (thiophene-2-carboxaldehyde and pyrrole-2-carboxaldehyde) with some derivatives of aminophenol (2-aminophenol, 2-amino 4-nitrophenol, 2-amino benzimidazole, or 2-amino 4-methylphenol) in hot methanol. Agar diffusion method was followed and minimum inhibitory concentration (MIC) established in assessing the antimicrobial property of the prepared ligands against the bacteria: *Salmonella typhi*, *Bacillus coagulans*, *Bacillus pumills*, *Escherichia coli*, *Bacillus circulans*, *Pseudomonas*, *Clostridium* and *Klebsilla pneumonia*.

Test compounds showed low to moderate activity to other strains studied as well and exhibited no cytotoxic effect against *Escherichia coli*. Compound **21** (Figure 3) was the most potent ligand with 17 mm diameter zone of inhibitory growth and MIC of 25 µg/mL against *Salmonella typhi*. The low bactericidal activity recorded for other ligands could be attributed to their interactions with the lipids content of the bacterial cell walls or their ribosomes content [44].

The pharmacological property of the candidate drugs is directly associated with the physiological conditions and chemical properties of both the test microorganisms and compounds. Thus, the penetration of candidate drugs through the cell membrane into the microbial cell may depend on

the degree of hydrophobicity. The same way that a polar molecule will dissolve a polar compound; the hydrophobic nature of the bacteria cell membrane will enhance the interaction with nonpolar compounds and favour their penetration into the cytoplasm resulting in cell death. Shanty and his colleagues [44] also noted the resistance of Gram-negative bacterium *Escherichia coli* against all prepared ligands due to the lipopolysaccharide protective layer of the bacterial cell membrane. This protective coat only allows for lipid soluble compounds interaction at the membrane surface and as such, reduces the amount of test compound flowing into the cell.

Heterocyclic Schiff bases consisting of 2-hydrazino-5-[substituted phenyl]-1,3,4-thiadiazole and 2-hydroxyacetophenone/benzaldehyde/indoline-2, 3-dione with their zinc(II) complexes have been successfully prepared and characterized by Singh *et al* [45].

The biological activity of the compounds and their corresponding metal complexes were studied. Bacteriostatic property by disc diffusion method and bactericidal activity by microdilution technique were selected to screen the effect of these compounds on bacteria. The antimicrobial activity of the metal-free ligands and the complexes was tested against *Bacillus subtilis* and *Escherichia coli*. All synthesized Schiff bases (Compounds **2.3-2.8**) possessed good antibacterial activity with increased potency observed in metal chelating ligands. Six 2-Chloro substituted ligands with their metal analogs (Compounds **2.3-2.8**) were more active (MIC 325-425 µg/mL), than other substituted ligands (MIC 330-455 µg/mL), against these microbes. Structure-activity relationship of the ligands revealed that the additional heterocyclic ring (indoline-2,3-dione) significantly increased the pharmacological potency of Compound **2.8** making it more active against all bacteria studied.

The *in vitro* antibacterial activities of novel tridentate Schiff bases and their cobalt(II) complexes were recently evaluated against five antibiotic-resistant strains, *i.e.*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Citrobacter amalonaticus* and *Klebsiella pneumoniae* following the disc diffusion method [46]. All tested compounds possessed antibacterial activity, showing considerable growth inhibitory zones against the isolates. Schiff bases and their complexes have no effect on *K. pneumoniae* strain from these extended spectrum β-lactamase isolates. For compounds **2.9** and **2.10** and their respective cobalt complex (Compound **2.11**) shows similar observations

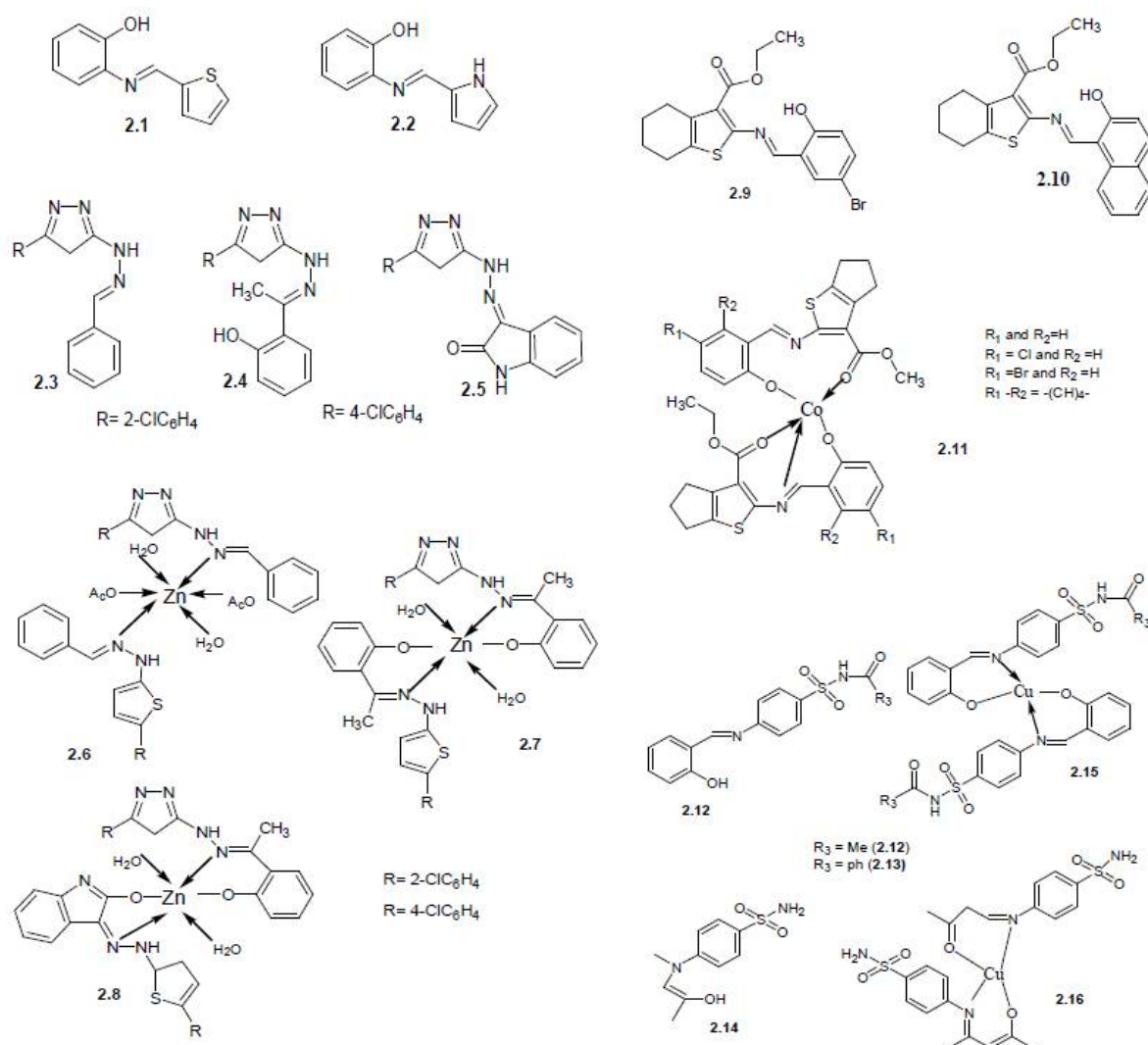


Figure 3: Chemical structures of some Schiff base compounds and their metal complexes with antibacterial activity

with metallo β -lactamase producing *P. mirabilis*, showing no zone of inhibition. The most sensitive strain was *Citrobacter amalonaticus*, with zones of inhibition ranging between $\phi 13$ and $\phi 22$ mm against cobalt complexes, produced by metallo β -lactamase. The enhanced antimicrobial activity of cobalt complexes against the tested isolates was attributed to the concept of chelation. Chelation increases the hydrophobic property of the ligand, achieved as positive charges on the metal are partially shared with the donor atoms present in the ligands which in turn favor π -electron delocalization over the metal complex formed. Hence, the lipophilic character of the metal complex increases and favors its permeation more efficiently through the lipid layer of the micro-organisms [46].

Schiff bases derived from sulphanilamide and related copper(II) complexes were synthesized by Saheli *et al* [47] and studied against Gram-positive (*Staphylococcus aureus* and

Enterococcus faecalis) and Gram-negative (*Klebsiella pneumoniae* and *Escherichia coli*) human pathogenic bacteria. The tested Schiff bases were obtained by refluxing sulfacetamide, sulfabenzamide and sulphanilamide with salicylaldehyde and acetylacetone in alcoholic solutions and by microdilution assay, MIC and minimum bactericidal concentration (MBC) of the ligands were evaluated together with their copper(II) based complexes with kanamycin as a positive control. The ligands (compounds 2.12 to 2.14) displayed the same potent antibacterial activity against tested strains with compound 2.13 standing out with the highest activity, recording a MIC 22.8 $\mu\text{g/mL}$. The activity of compound 2.13 improved on complexation (compound 2.15) as it discloses a 2-fold strength (MIC, 11.4 - 22.8 $\mu\text{g/mL}$) against the strains. Compound 2.16 has a broad spectrum activity inducing bacteria cell death.

The increased potency of Schiff base compounds after metal chelation can be explained by the Overtone's concept [48] and the Tweedy's theory [49]. The theory describes that chelation reduces the polarity of metal ions to a greater extent due to the overlapping of the ligand orbital and partial sharing of positive charge of the metal ion with donor groups and delocalization of electron into the whole chelate ring [50]. Another important factor controlling antimicrobial activity is lipophilicity. High lipophilicity generally leads to compounds with high rapid turnover [51]. As lipophilicity increases so do cell membrane permeability, which may result in an alteration in cellular metabolic activities and cytoplasmic leakage leading to cell death.

Antifungal activity

Fungi are plant pathogens, cause a wide range of diseases and are also the principal sources of secondary metabolites including mycotoxins [52]. Food contamination by fungi and attendant mycotoxins pose a threat to human and animal health and also compromise the economy seriously. Physical and biological approaches include heat treatment, washing, the use of bacteria and enzymes. Fungi and mycotoxins degradation are used to control fungal propagation [53]. The use of inorganic compounds such as silica-based materials, *i.e.*, binders and their chemical modifications to mitigate fungal contamination have been documented [54,55]. However, their health implications and appearances in commodities often compromise food quality. For these reasons, the continuous need to develop novel compounds against microbial resistance to commercial standard drugs cannot be overemphasized.

Recently, Maddila *et al* reported on the synthesis and antifungal activity of new Schiff bases derived from benzothiazole pyrimidine derivatives.[56] Broth dilution method was used to determine the MIC of the ligands on *Aspergillus flavus*, *A. fumigatus*, *Candida albicans*, *Penicillium marneffeii* and *P. mucor*. All tested organisms were sensitive to the ligands that exhibited mildly to good antifungal activity at a concentration range of 100 – 200 µg/mL. It was observed that the *para*-substitution was preferred to *ortho* substitution. Compounds **2.1-19** (Figure 4) exhibited the same if not, greater antifungal activity (MIC 12.5 - 25 µg/mL) when compared to ciprofloxacin (MIC 12.5-50 µg/mL) used as a standard. The abundance of aromatic rings contained in these compounds with electron-withdrawing substituents disclosed their

biological importance over compounds studied under similar conditions. From the seven Schiff base ligands prepared, compound **2.18** was the most potent, affecting the metabolic activity of all tested fungal strains. Compound **2.18** displayed greater activity (MIC 12.5 µg/mL) than standard drug clotrimazole (MIC 25 µg/mL) against tested strains. These results present the ligand to be two against *A. flavus* and *A. fumigatus* and four times more potent against *C. albicans* and *P. mucor* than clotrimazole. *The potency of the compound* could be directly associated with high lipophilicity indexes ranging between 5.4 - 6.17 [29].

The antifungal activity of a series of Schiff bases derived from 1,3-benzothiazole-2-yl-hydrazones was evaluated against *Aspergillus niger*, *Rhizopus oryzae* and *Candida albicans* following the disc diffusion method [57]. All compounds were prepared in hot ethanol by mixing 6-chloro-2-benzothiazol-2-yl-hydrazine with different aromatic carbonyls. Compound **2.20** and **2.21** (Figure 4), amongst others, showed similar activities against *A. niger*, whereas Compound **2.20** was highly potent against *Rhizopus oryzae* and *Candida albicans*. The improved activity of these compounds is due to the substitution of electron donating group (-CH₃) in *para* position and electron withdrawing group (-NO₂ and -Br) in the same position.

Schiff bases derived from glycylglycine with imidazole-2-carboxaldehyde and indole-3-carboxaldehyde and their zinc(II) complexes were synthesized and assessed for their antifungal activities [58]. The ability of the ligands and their complexes to induce fungal cell death following disc diffusion method was studied against *A. niger*, *A. flavus*, *Rhizopus stolonifer*, *Rhizoctonia bataicola* and *C. albicans* with nystatin used as a standard antifungal drug. *In vitro* antifungal analysis showed moderate activity against the tested strains [58]. Compound **2.22** (Figure 4) showed low activity against *A. niger* as compared to its analog Compound **2.23**. Zn(II) complexes of the ligands (**2.24** and **2.25**) (Figure 4) showed higher activity compared to the free ligands. The uncoordinated atoms with the ligands enhance the activity of the complexes. Zinc ion increased the fungistatic property of the parent ligands as it binds easily at the cell wall membrane and, therefore, alters the cell's life and inhibits translation, which result in limited cell growth or cell death [59]. Chelation significantly reduced the polarity of Zn(II) ion by sharing its positive charge with ligand's electron donor groups, hence, increases the compound's permeability through the bacterial cell membrane into the cell.

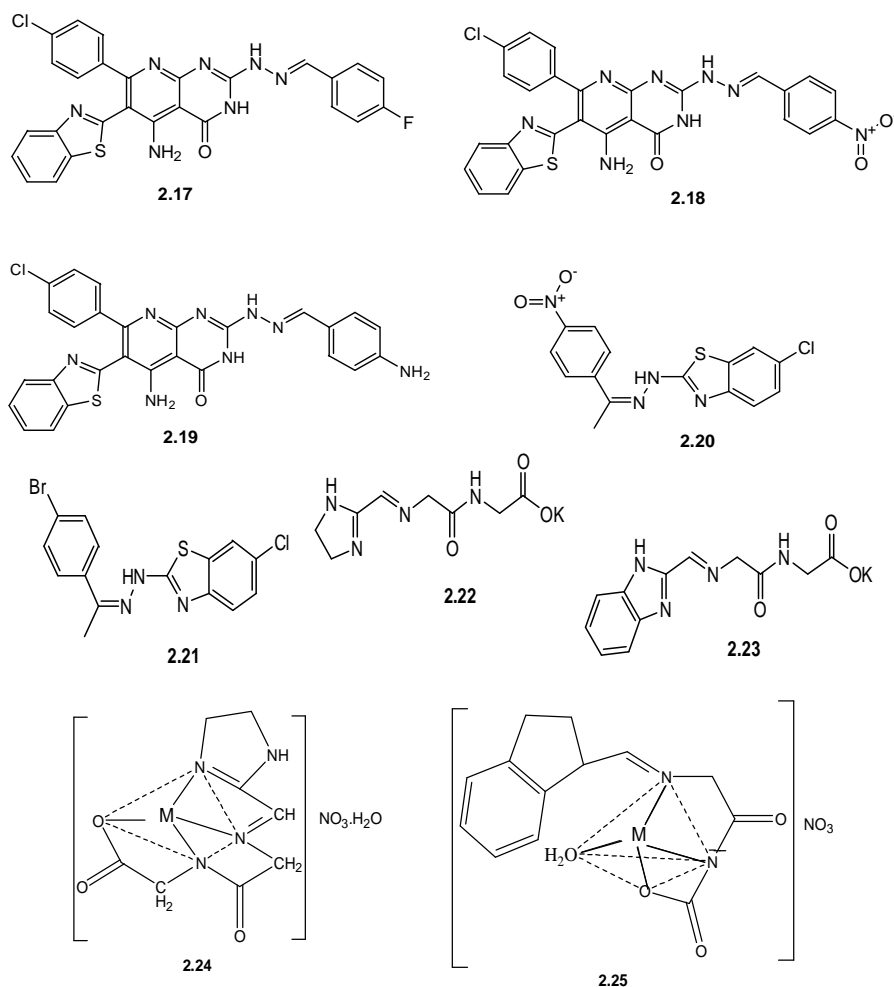


Figure 4: Chemical structures of some Schiff base compounds and their metal complexes with antifungal activity

Antimalarial activity

Over 40 % of the world's population is exposed to malaria parasites due to increase of vectors' resistance to pesticides, the spread of drug-resistant malaria parasites, and the toxicity of current antimalarial drugs, thus stimulating the need to develop effective novel and less toxic antimalarial drugs with different mechanisms of action. Azomethine (C=N) contained compounds are potential molecules that alleviate the problem of drug resistance. Schiff bases derived from sulphonamide and its derivatives together with those containing thiosemicarbazone moieties have been reported as good antimalarial parasites [60,61].

A series of fifteen Schiff bases derived from aromatic sulphonamides and analogs have been screened as inhibitors of *Plasmodium falciparum* carbonic anhydrase enzyme, indispensable to the biosynthetic pathway of pyrimidine, whose metabolic activity in malaria parasites can be found here [62]. The effect of these Schiff bases on *Plasmodium* enzyme was studied and the activity was compared to clinical drug acetazolamide. Authors suggested that the

antimalarial activity of the compounds depended mainly on the nature of the substituted aromatic aldehydes used in the formation of the ligands. Sulphonamide derived Schiff bases with substituted (2-methoxyphenyl-; 2- or 4-chlorophenyl-; 2- or 4-hydroxyphenyl- and 3-methoxy-4-hydroxy-5-bromophenyl) aldehydes were very potent inhibitors of carbonic anhydrase enzyme, among others. Compounds **2.26-2.29** (Figure 5) inhibited parasite activity with an affinity constant (K_i) ranging from 0.54-1.23 $\mu\text{g/mL}$, whereas, Compounds **2.30** and **2.32** (Figure 5) were the most potent derivatives with K_i between 80 to 0.5 ng/mL against carbonic anhydrase enzyme. The unsubstituted compound **2.31** also displayed good antimalarial activity. At K_i (80 ng/mL), the compounds were four times more effective when compared to acetazolamide (K_i , 315 ng/mL).

Antimalarial activity of a series of Schiff base compounds with hydrazine scaffold obtained by a condensation reaction between hydrated hydrazine and different aldehydes was studied against chloroquine-sensitive strain 3D7 and the chloroquine-resistant K1 strain of *Plasmodium*

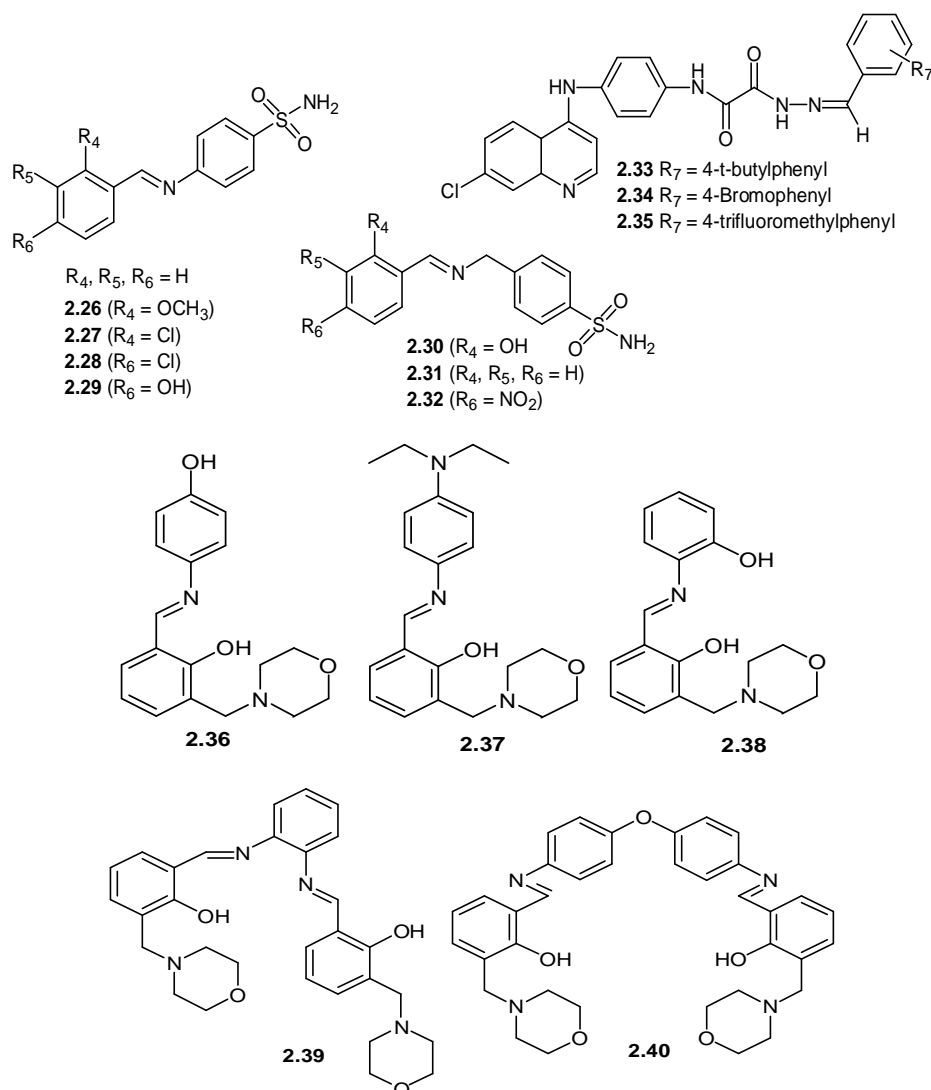


Figure 5: Chemical structures of some selected antimalarial Schiff base compounds

falciparum with chloroquine used as a reference antiplasmodial drug [63]. The studied compounds displayed good activity when compared to chloroquine.

Compounds **2.33**, **2.34** and **2.35** (Figure 5) showed good antimalarial activity against the tested 3D7 strain with IC_{50} ranging from 19.69 to 25.38 ng/mL.

Compound **2.33** was highly cytotoxic to the parasites with IC_{50} 19.69 and 51.96 ng/mL, respectively, when compared to chloroquine (IC_{50} 495.94 ng/mL). Its analogs, compounds **2.34** and **2.35** exhibited similar potency against malaria parasites, inducing cell death at IC_{50} of 20.78 and 85.68 ng/mL and IC_{50} of 25.38 and 22.52 ng/mL against strains 3D7 and K1, respectively. Structure-activity relationship of the ligands disclosed that the higher antiplasmodial activity of the ligands against the parasites was conferred to the t-butyl group in *para* of arylidene

moiety (**2.33**), the 4-bromo- (**2.34**) and 4-trifluoromethyl-substituted (**2.35**) compounds. The highly hydrophobic nature of these ligands induced by the aliphatic moieties increases their lipophilicity properties and facilitates their movement across the bilayer membrane. These observations encourage the search for novel antimalarial agents with substituted arylidene and heterocycles.

Jarrahpour *et al* [64] reported the synthesis and biological application of novel Schiff bases bearing morpholine scaffold. The compounds were prepared in hot ethanol as a mixture of 2-hydroxy-3-(morphinomethyl) benzaldehyde with some mono and bis-aromatic amines. The *in vitro* antimalarial activity of the ligands was investigated against chloroquine-resistant *P. falciparum* K14 following the broth microdilution assay. Data recorded showed that compounds **2.36** - **2.40** (Figure 5) were very active, inhibiting the growth of this parasite and exhibited good to

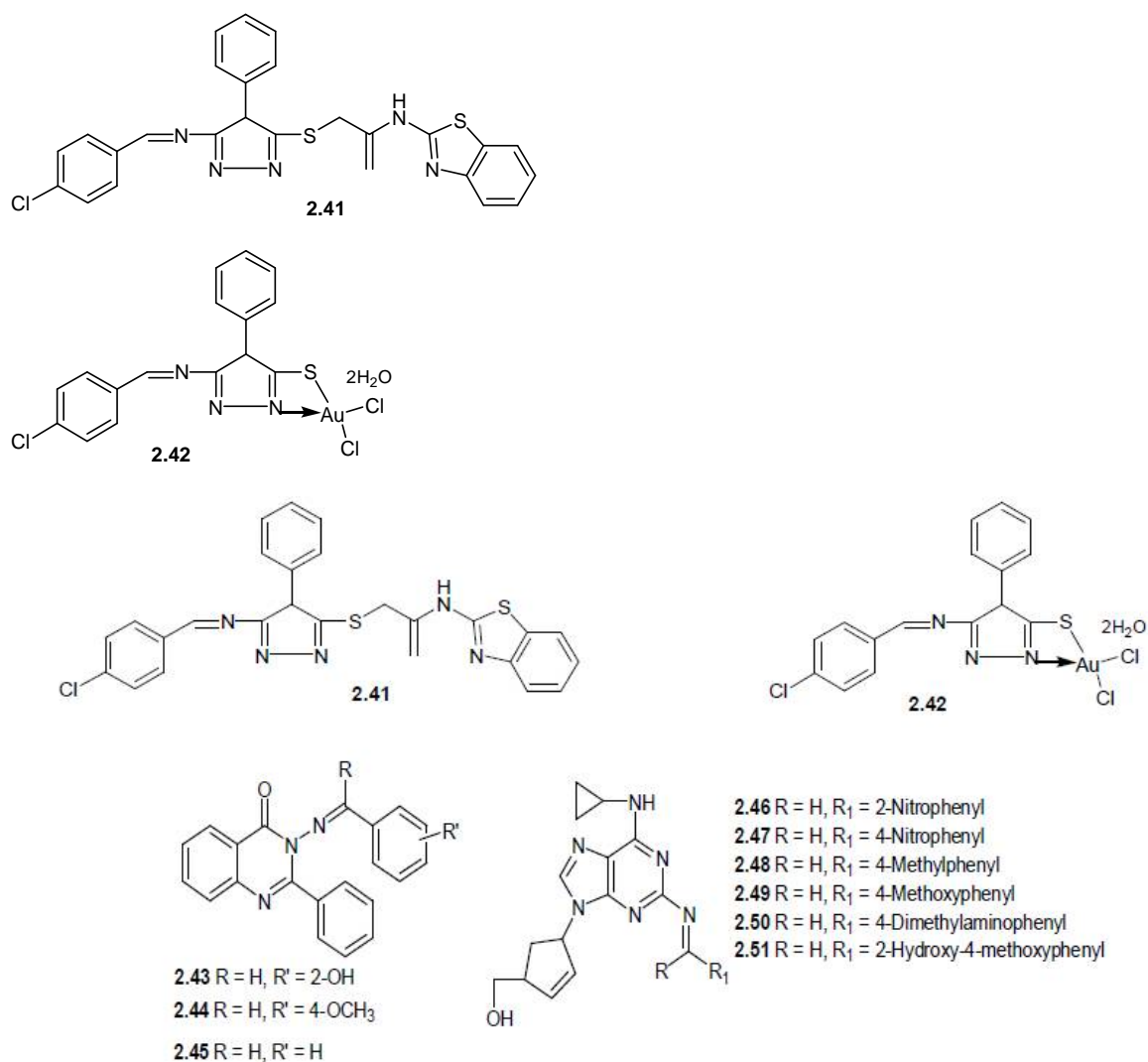


Figure 6: Chemical structures of some selected antiviral Schiff bases and their complexes

excellent antimalarial activity (IC_{50} , 2.28 - 26.9 $\mu\text{g/mL}$). Compound **2.38** was the most potent antimalarial agent (IC_{50} 2.28 $\mu\text{g/mL}$), extending the benefits of morpholine ring in biological applications.

Antiviral activity

Viruses, with the exception of some few microorganisms that differ from prokaryotes and eukaryotes, have their genetic materials stored in ribonucleic acids (RNA) and not in deoxyribonucleic acids (DNA). Drug resistance by viruses is a serious public health issue and treatment of related infections calls for the search for novel bioactive compounds in addressing the problem.

A series of Schiff base ligands derived from 5-amino-4-phenyl-4H-1,2,4-triazole-3-thiol and their metal complexes have been synthesized and evaluated for their antiviral properties. For example, Al-Masoudi *et al* [65] reported on the

synthesis and antiviral activity of some Schiff bases against HIV-1 (strain IIIB) and HIV-2 (strain ROD) in human T-lymphocyte (MT-4) cells using the MT-4/MTT assay. The EC_{50} (effective concentration of compound (μM) achieving 50% protection in MT-4 cell lines against the cytopathic effect of HIV) was established. It was found that tested strains were sensitive to the ligands and their complexes with greater activity observed in metal-based ligands. Compounds **2.41** and **2.42** (Figure 6) were the most potent anti-HIV agents studied from this series inhibiting replication in cell culture at EC_{50} 10.2 $\mu\text{g/mL}$ against HIV-2 with an index selectivity of 9. Gold complex, compound **2.42** displayed higher antiviral activity than other complexes probably because gold has some antimicrobial property and Tweedy's theory may have as well influenced the membrane permeability.

Kumar *et al* [66] synthesized Schiff bases of 3-(benzylideneamino)-2-phenylquinazoline-4(3H)-ones through the formation of 3-amino-2-phenyl

quinazoline-4(3H)-one with various substituted carbonyl compounds. Antiviral activity against different viruses viz: herpes simplex virus-1 (KOS), herpes simplex virus-2, vaccinia virus, vesicular stomatitis virus, herpes simplex virus-1 TK- KOS ACVr, para influenza-3 virus, reovirus-1, Sindbis virus, and seven others were carried out. The efficacy of the ligands to alter the process of respiration in each viral representative was compared to brivudine, ribavirin, cidofovir, ganciclovir used as reference materials.

The studied microorganisms reacted differently when exposed to the test compounds with some displaying more sensitivity to the prepared Schiff bases than the controls. Herpes simplex virus-1, herpes simplex virus-2, herpes simplex virus-1 and vaccinia virus in human embryonic lung cell culture were very sensitive to compound **2.43** (Figure 6) exhibiting 50 % cell death at EC₅₀ ranged of 0.8 - 30 µg/mL greater than the positive controls (EC₅₀, 0.05 - 250 µg/mL). The methoxy-substituted (**2.44**) and unsubstituted (**2.45**) analogs of compound **2.43** also exhibited better antiviral properties in comparison to the standards.

A study by Sriram *et al* [67] described the synthesis of Schiff bases derived from abacavir prodrugs with substituted benzaldehyde and ketone derivatives using microwave irradiation. The ability of the compounds to inhibit the replication of HIV-1 in CEM cell lines and EC₅₀ and CC₅₀ (cytotoxic concentration of compound (µM) required to reduce the viability of mock-infected CEM cells by 50%) were determined. Abacavir and synthesized ligands exhibited excellent anti-HIV activity, particularly compounds **2.43** - **2.51** were found to be highly active against HIV. Substituted benzaldehyde derivatives were more active than ketone analogs. Compound **2.48** displayed the strongest inhibitory property with EC₅₀ of 0.05 µM, CC₅₀ > 100 µM, a selectivity index (SI) > 2000, and observed to be 32 times more potent than the parent drug (EC₅₀, 1.6 µM). It was also recorded that the lipophilicity of the ligands significantly increased their pharmacological properties.

CONCLUSION

Undoubtedly, Schiff bases have good biological properties and the ability of heteroatoms containing Schiff bases to form complexes with metal ions is an added advantage to their pharmacophore properties. It is necessary to bring together those Schiff bases and metal-based Schiff base compounds that have demonstrated significant biological properties for modification towards future drug development as

microorganisms turn to nullify the effectiveness of current antibiotics and antimicrobial agents through resistance and adaptation.

DECLARATIONS

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Conflict of interest

The authors declare no conflict of interests.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. In addition, a declaration of the role of each author is as provided. Mr. Thierry Y Fonkui put the manuscript all together and wrote the initial draft of the paper, Dr. Monisola I Ikhile conceived and co-supervised the study; Professors Derek T Ndinteh and Patrick B Njobeh designed, supervised and edited the work. All authors read and approved the manuscript for publication.

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