REVIEW ON SCHIFFS BASE DERIVATIVES

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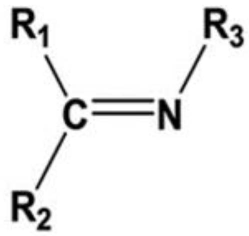
Abstract- Researchers' interest in Schiff bases prepared from ortho-hydroxyl aromatic aldehydes is due to their ability to act as bidentate ligands for transitional metal ions. Later, in studies, it has been observed that azomethines from salicylaldehydes gave the best quantitative structure-antitumor activity relationship which has been studied for a series of Schiff bases derived from a variety of substituted aromatic amines and aldehydes (6). Schiff bases are active against many organisms such as Erysiphe graminis, Bacillus polymxa, Staphylococcus aureus, Candida albicans, Escherichia coli, Trychophytongypseum, Plasmoporaviticola, and Mycobacteria. They have shown excellent stability, and selectivity for specific metal ions such as Pb (II), Co (II), Al (III), Ag (II), Gd (III), Cu (II), Ni (II), Y(III), Zn (II), and Hg (II), so that large number of different Schiff base ligands have been used in potentiometric sensors as cation carriers. The principal interaction between the metal surface and inhibitor is Chemisorption. The inhibitor molecule should have centers that can form bonds with the metal surface by electron transfer. In such cases, the inhibitor acts as a Lewis base and the metal acts as an electrophile.

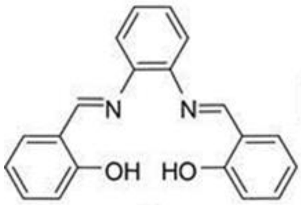
***Keywords*: schiffs base, structure activity relationship, antiviral activity, basicity**

INTRODUCTION

In the year 1864, Hugo Schiff was the first to synthesize Schiff's base under azeotropic distillation by using aldehyde or ketone and primary amine. They can be considered a sub-class of imines with the general structure R1R2C·NR′ (R′ ≠ H) (1-3). Depending on their structure, they can be considered as either secondary aldimines or secondary ketimines. When these compounds are being used as ligands to form coordination complexes with metal ions, the term Schiff base is applied. Corrin complexes occur naturally, but the majority of artificial Schiff bases are used to form many important catalysts, such as Jacobsen's catalyst. Schiff bases are imines in which R3 is an alkyl or aryl group (not hydrogen). R1 and R2 may be hydrogen. Schiff bases have a wide range of biological properties such as antimicrobial, anticancer, and antiviral. Inhibition of amyloid-β aggregation is achieved by Schiff bases(4). They are common enzymatic intermediates where an aldehyde or ketone of a cofactor or substrate reversibly reacts with the terminal group of a lysine residue. Lysine residue forms a Schiff base with the common enzyme cofactor pyridoxal phosphate (PLP) and is transaldiminated to the substrate(s). Similarly, the cofactor retinal forms a Schiff base in human rhodopsin (via Lysine 296), which is key in the photoreception mechanism. In coordination chemistry, Schiff bases are common ligands. The ligands are derived from aromatic aldehydes and alkyl diamines(5). The imine nitrogen is basic in nature and exhibits pi-acceptor properties. In 1968, RyōjiNoyori was awarded a share of the 2001 Nobel Prize in Chemistry for the development of a copper-Schiff base complex for the metal-carbenoid cyclopropanation of styrene.



R_1, R_2 and / or R_3=alkyl or aryl



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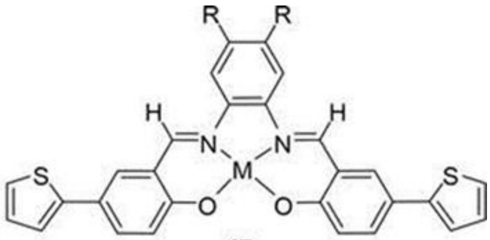

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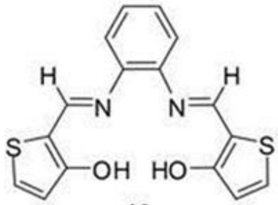
R = -H, $-OC_6H_{13}$, $-OC_{12}H_{25}$
M = V, Ni, Cu



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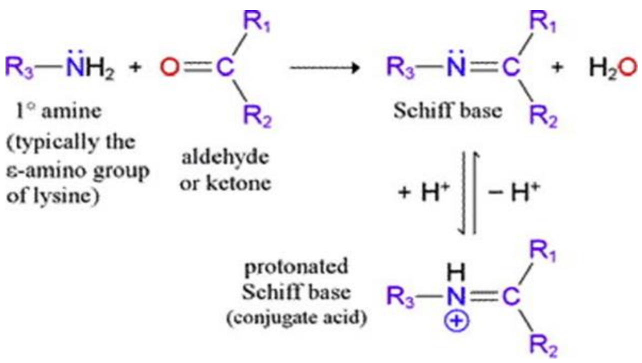
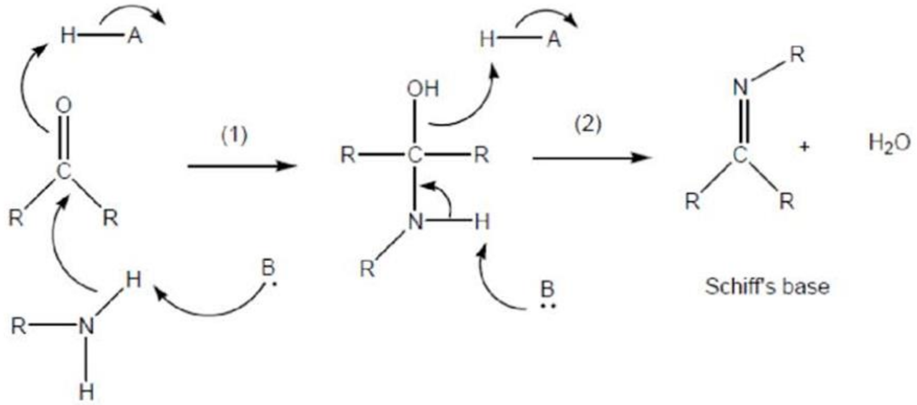
Schiff base ligands

Researchers' interest in Schiff bases prepared from ortho-hydroxyl aromatic aldehydes is due to their ability to act as bidentate ligands for transitional metal ions. Later, in studies, it has been observed that azomethines from salicylaldehydes gave the best quantitative structure-antitumor activity relationship which has been studied for a series of Schiff bases derived from a variety of substituted aromatic amines and aldehydes(6). Schiff bases are active against many organisms such as Erysiphe graminis, Bacillus polymxa, Staphylococcus aureus, Candida albicans, Escherichia coli, Trychophytongypseum, Plasmoporaviticola, and Mycobacteria. They have shown excellent stability, and selectivity for specific metal ions such as Pb (II), Co (II), Al (III), Ag (II), Gd (III), Cu (II), Ni (II), Y(III), Zn (II), and Hg (II), so that large number of different Schiff base ligands have been used in potentiometric sensors as cation carriers. The principal interaction between the metal surface and inhibitor is Chemisorption. The inhibitor molecule should have centers that can form bonds with the metal surface by electron transfer. In such cases, the inhibitor acts as a Lewis base and the metal acts as an electrophile. The protective compound has oxygen and nitrogen atoms with free electron pairs which are readily available for sharing and serves as a nucleophilic center. They create multiple absorption sites for the inhibitor along with the atoms of the benzene rings thus enabling stable monolayer formation(7).

SYNTHESIS

The first imines were synthesized in the nineteenth century by Hugo Schiff in 1864. Since then, a variety of methods have been developed for the synthesis of imines. The classical synthesis involves the condensation of a carbonyl compound with an amine under azeotropic distillation reported by Schiff. Water formed in the system was completely removed by using a molecular sieve(8). An in-situ method for water elimination was developed using dehydrating solvents such as tetramethyl orthosilicate or trimethyl orthoformate in the 1990s. Chakraborti et al. demonstrated that the efficiency of these methods is dependent on the use of highly electrophilic carbonyl compounds and strongly nucleophilic amines. Schiff bases are often polydentate in coordinating ability, because of synthetic flexibility, the special property of C·N group and the relative ease of preparation, especially when ·SH or ·OH are present close to the azomethine group which can form a five or six membered ring with the metal ion.





Denticity and basicity of Schiff base

The Schiff base ligands are classified according to the number of donor atoms and are named as uni-, di-, tri-, and tetra-dentate ligands. Schiff bases possess nitrogen donor atoms, so can act as bi-, tri-, tetra- or polydentate ligand. In general, the donor nature of the ligand depends both on the type of aldehyde/ketone used and the nature of primary amine/diamine.

The basicity of the Schiff base also plays a key role in the formation and stabilization of the complexes. The ·OH group present in the Schiff base can induce tautomerism in the compound, which leads to a compound with different structures. A large number of Schiff base compound show keto-enol tautomerism. Also, the deprotonation of alcoholic and phenolic groups is favored due to the stabilization of various oxidation states of different metal ions. Coordination with transition metal Schiff base metal complexes is prepared in situ by producing a reaction between the Schiff base and well-defined metal. This approach is clearly simple and suitable for catalytic applications. Different concentrations of different complexes can be present, when an equilibrium constant is expressed as a concentration quotient. However, the identity and homogeneity of the complex can be controlled by the introduction of a bulky group in the Schiff bases due to the shifting of the equilibrium toward the formation of a single species. A disproportionation between Schiff base metal complexes and the metal alkoxides can occur and the stability of the complexes is regulated by the equilibrium constant.

Schiff base ligands are able to coordinate many different metals with various oxidation states, enabling the use of Schiff base metal complexes for a large variety of useful catalytic transformations. Schiff-base ligands containing imidazole groups have potential donor and acceptor character in the formation of a coordination bond and function as a ligand-complex or as a self-complementary building block for the construction of the assembly structure due to the formation of a coordination bond with Cu (II) ions(9). The versatility of Schiff base ligands and the biological, analytical, and industrial applications of their complexes have promoted further investigations in this area. The importance of Schiff base complexes for bioinorganic chemistry, biomedical applications, supramolecular chemistry, catalysis and material science, separation and encapsulation processes, and formation of compounds with unusual properties and structures has been well recognized and reviewed. A large number of Schiff bases and their complexes are of significant attention because of their biological activity including antitumor, antibacterial, fungicidal, and anticarcinogenic properties and catalytic activity(10).

APPLICATIONS

Antimalarial activity

Malaria is a neglected disease that still causes serious publichealth problems. Every year, approximately 500 million people are afflicted by the disease, of whom around 1–3 million die,90% of who in sub-Sahara Africa are primarily children .[11]Malaria is currently found in more than 100 countriesthroughout Africa, Latin America, Asia, and Oceania. Humanmalaria is mainly caused by four species of Plasmodium (P. fal-ciparum, P. vivax, P. ovale, and P. malariae). The female mosquito of the Anopheles genus is the vector of Plasmodium [12].The search for new drugs, vaccines, and insecticides to preventor treat this disease is clearly a priority.Schiff bases have been shown to be interesting moieties forthe design of antimalarial agents. Ancistrocladidine is a secondary metabolite produced by plants from the familiesAncistrocladaceae and Dioncophyllaceae that present an iminegroup in its molecular scaffold. Compound 1 has been shownto be active against P. falciparum K1 and 3D7. The minimuminhibitory concentrations (MIC values) of ancistrocladidinenecessary to completely abolish P. falciparum K1 and 3D7growth were 0.3 and 1.9 lg/mL, respectively. Interestingly,compound 1 was 90- and 10-fold more selective to P. falcipa-rum K1 and 3D7,respectively than to rat skeletal myoblastL-6 cells . Rathelot et al. [13] described the synthesis ofSchiff base-functionalised 5-nitroisoquinolines and investigated the in vitro activity of these compounds against anACC Niger chloroquine resistant P. falciparum strain. Schiffbase was the most effective antimalarial agent amongthe synthesised 5-nitroisoquinoline derivatives. The concentration of compound 5 necessary to inhibit P. falciparum growthby 50% (IC50) was 0.7 lg/mL. Under the same experimentalconditions the IC50 value for chloroquine was 0.1 lg/mL [13]

Antibacterial activity

The increase in the mortality rate associated with infectiousdiseases is directly related to bacteria that exhibit multipleresistance to antibiotics. The lack of effective treatments isthe main cause of this problem[14,15] . The development ofnew antibacterial agents with novel and more efficient mechanisms of action is definitely an urgent medical need[16].Schiff bases have been pointed to as promising antibacterialagents. For example, N-(salicylidene)-2-hydroxyanilineis effective against Mycobacterium tuberculosisH37Rv, exhibiting an MIC value of 8 lg/mL. The selectivity of compound 4 was checked by performing experimentswith J774 macrophages. No cytotoxic effect on J774 macrophages was observed for compound 4, even when it was testedat concentrations as high as 1000 lg/mL. More than 80% ofmacrophage cells were viable at such experimental conditions,demonstrating the high selectivity of compound 4.The synthesis and antimicrobial activity of a series of Schiffbases derived from the condensation of 5-chloro-salicylalde-hyde and primary amines has recently been reported.[17]The 5-chloro-salicylaldehyde-Shiff base derivatives were most active against at least one of the evaluatedbacterial species. Pseudomonas fluorescence was the strain mostsensitive to compounds 6–11 and 13–15, with MIC valuesranging from 2.5 to 5.2 lg/mL. The MIC value for the reference drug kanamycin against the same bacterial strain was3.9 lg/mL. The Schiff bases 6, 7, 9–11, 14, and 15 presentedMIC values in the range of 1.6–5.7 lg/mL against Escherichiacoli, while the MIC value for kanamycin was 3.9 lg/mL. Bacil-lus subtilis was sensitive to the Schiff base 14 only(MIC = 1.8 lg/mL). The MIC values for compounds 6 and7 against Staphylococcus aureus were, respectively, 3.1 and1.6 lg/mL .[17]Isatin-derived Schiff bases have also been reported to possess antibacterial activity . [18]Twenty-eight bacteria of clinicalinterest were used in the studies performed by Pandeya andcolleagues. The authors disclosed the isatin-derived Schiff base16 (Fig. 3) as the most potent compound amongst those synthesised against all the pathogenic bacteria studied. The MICvalues for compound 16 against E. coli NCTC 10418, Vibriocholerae non-01, Enterococcus faecalis, Proteus shigelloideswere 2.4, 0.3, 1.2, and 4.9 lg/mL, respectively, while theMIC values for sulfamethoxazole (reference drug) against thesame bacterial strains were in the range of 312–5000 lg/mL.Thus compound 16 was notably 1040-, 1040-, 4160-, and1020-fold more potent than sulphamethoxazole. Other isatin-derived Schiff bases have been described in the literature, butwith no expressive antibacterial activities [19,20]The isoniazid-derived Schiff base 17 was activeagainst M. tuberculosis H37Rv, exhibiting an MIC value of0.03 mg/L.[21] In this respect, compound 17 was slightly morepotent than isoniazid, its immediate synthetic precursor. Additionally, the isoniazid-derived Schiff base 17 was not toxicagainst the cell line VERO (epithelial cells from healthy monkey kidney). The IC50 for compound 17 against VERO cellswas as high as 1 g/mL, indicating that this isoniazid-derivedSchiff base is selective for bacterial cells. The therapeutic safetyand effectiveness for compound 17 is higher than 40,000, making this Schiff base an excellent lead for the development ofantitubercular agents [21].In 2005, Panneerselvam et al. described the synthesisand in vitro antibacterial activity of eleven morpholine-derivedSchiff bases. shows the chemical structure of three ofthem (compounds 18–20). The authors found that S. aureusMicrococcus luteus were the bacteria most sensitive tothe morpholine-derived Schiff base 18 (MIC = 20 and 32 lg/mL, respectively). Streptococcus epidermidis was more sensitiveto the morpholine-derived Schiff base 19 (MIC = 17 lg/mL)and Bacillus cereus and E. coli were more sensitive to compound 20 (MIC = 21 and 16 lg/mL, respectively).Schiff bases with a 2,4-dichloro-5-fluorophenyl moiety arealso effective in the inhibition of bacterial growth. Schiff basesfrom this class completely inhibited the growth of S. aureus, E. coli, Pseudomonas aeruginosa,and Klebsiella pneumoniae. MIC values for these compounds varied from 6.3 to 12.5 lg/mL, which are comparableto those obtained for the reference drug ciprofloxacin [22].Madurahydroxy lactone Schiff bases are imines derivedfrom natural products. Madurahydroxylactones are secondarymetabolites produced by the plant Actinomadura rubra .[23]The imines 25–30are examples of Schiff bases belong-ing to this class. With the exception of compounds 25 and 30,all Madurahydroxylactone-derived compounds were effectivein the in vitro inhibition of B. subtilis, Micrococcus flavus, Sarcina lutea, and S. aureus growth, with MIC values varyingfrom 0.2 to 3.1 lg/mL .[24] These same compounds (26–29)presented very low activity against Mycobacterium phlei orProteus vulgaris (MIC values higher than >50.0 lg/mL) [24].Other molecules of natural or non-natural origin that areplatforms for the synthesis of Schiff bases for antibacterialactivities include amino acids, coumarins, sulfonamides, or resacetophenones, aminothiazolyl bromocoumarins, crownethers, O-phthaldehyde, or 2-aminophenol and 1,2,4-triazoles[25,31]. The antibacterial property of compounds representative of these classes was examined. However, they did not exhibit any notable activity.

Antifungal activity

Fungal infections are not usually limited to the superficial tissues; indeed, a significant increase in life threatening systemicfungal infections has been reported [32] The fundamental reason for this is the increasing number of patients at risk, includingthose with advanced age, major surgery, immunosuppressivetherapy, acquired immunodeficiency syndrome (AIDS), cancertreatment, and solid-organ and hematopoietic stem cell transplantation [33] The search and development of more effectiveantifungal agents are mandatory [34,35]and some Schiff basesare known to be promising antifungal agents.Alternaria brassicae and Alternaria brassicicola are phytopathogenic fungi that severely affect the production of mostcruciferous crops (broccoli, cauliflower, mustard, turnip, cabbage, rape, and radish). N-(Salicylidene)-2-hydroxyaniline 4(Fig. 2) at the concentration of 500 ppm inhibited the growthof these fungi by 67–68% [36]. Compounds 2 and 3 are examples of chitosan-derived Schiff bases with antifungalactivity. They inhibited the growth of Botrytis cinerea and Colletotrichum lagenarium by 26–33% and 35–38% when used at1000 ppm, respectively [36] Overall, studies evaluating the effect of Schiff bases on phytopathogenic fungal growth havebeen modest and deserve more investigation.Schiff bases with a 2,4-dichloro-5-fluorophenyl moiety, suchas compounds 21 and 31–34 have been demonstrated to inhibit the growth of fungi of clinical interest, such asAspergillus fumigatus, Aspergillus flavus, Trichophyton mentagrophytes, and Penicillium marneffei. The MIC values forthese compounds were in the range of 6.3–12.5 lg/mL, indicat-ing that they are as potent as the reference fluconazole [22]Piperonyl-derived Schiff bases were activeagainst some fungi at micromolar concentrations. They inhibited the growth of Trichophyton rubrum (MIC = 820–980 lM)and Epidermophyton floccosum (MIC = 200–930 lM)[37] .The isatin-derived Schiff bases and 41–51 were considerably active against Microsporum audouinii(MIC values ranging from 2.4 to 9.7 lg/mL) and Microsporumgypseum (MIC values ranging from 1.2 to 9.7 lg/mL).Compounds 16 and 41–51 also inhibited the growth of Candida albicans, Aspergillus niger, Cryptococcus neoformans, T.mentagrophytes, E. floccosum, and Histoplasma capsulatum atMIC values higher than 10 lg/mL and lower than 79 lg/mL. In another study, Panneerselvam et al.showed thatthe growth of both C. albicans and A. niger was compromisedby treatment with compound 20 at20 lg/mL or compound 52 at30 lg/mL.As for antibacterial activity, natural product-derived Schiffbases are also promising for the design of new antifungalagents. Domb and colleagues have described an interesting ap-proach to synthesize a nystatin-dextran-derived Schiff base. This approach dramatically improved nystatin solubility in water [37]. Compound 53 completely inhibited thegrowth of C. albicans and C. neoformans at 20 lg/mL, whilea concentration of 10 lg/mL was required for free nystatinto have a similar effect. Although the nystatin-dextran-derivedSchiff base 53 was less active than nystatin itself, the formerwas shown to be much less toxic to normal cells .[37]

Antiviral activity

The use of vaccines may lead to the eradication of viral pathogens, such as smallpox, polio, and rubella. However, virus-related and hepatitis C human immunodeficiency diseases havebeen the drawback of vaccine approaches [38]. Viral diseasesare life-threatening for immunocompromised patients and aprompt treatment is required to overcome this problem.Although there are many therapeutic options for viral infec-tions, currently available antiviral agents are not yet fullyeffective, probably due to the high rate of virus mutation. Theymay also present any of a number of side effects.Salicylaldehyde Schiff bases of 1-amino-3-hydroxyguanidine tosylate are a good platform for the design of new antiviral agents[39,40] . In fact, from a set of different 1-amino-3hydroxyguanidine tosylate-derived Schiff bases, compound54 was shown to be very effective against mouse hepatitis virus (MHV), inhibiting its growth by 50% when employed at concentrations as low as 3.2 lM[40] .Recently, Sriram and colleagues reported[40] the synthesisand antiviral activity of the abacavir-derived Schiff bases 55–65. These compounds are a new series of abacavir prodrugs. Abacavir is a nucleoside analogue capable of inhibitingthe activity of reverse transcriptase. It is used to treat humanimmunodeficiency virus (HIV) and AIDS, and is available un-der the trade name Ziagen (GlaxoSmithKline). Compounds55–65 were significantly effective against the human immune deficiency virus-type 1 (HIV-1). The effective concentration(EC50) of these abacavir-derived Schiff bases necessary toachieve 50% protection of human leukemic cells (CEM) againstthe cytopathic effect of HIV-1 was lower than 6 lM [40]. Nota-bly, compound 57 was the most potent Schiff base, being effective at 50 nM. This compound is only toxic to CEM cells atconcentrations higher than 100 lM, indicating its potential asa lead compound for the design oanti-HI[41]

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