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# Schiff Bases and Their Metallic Derivatives: Highly Versatile Molecules with Biological and Abiological Perspective

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## Abstract

1998 onwards, a span reporting thousands of research articles describes the ever-increasing applicability of Schiff bases and their metallic complexes; this chapter comprehensively examines the literature of the last 20 years. The structural diversity of these molecules made them available for a very wide range of biological and abiological applications. Schiff bases are excellent chelators and due to this unique property have found their place in qualitative and quantitative determination of metals in aqueous media. The structural diversity of metal chelates proved these to be outstanding catalysts and displayed interesting fluorescence effect. Finally, Schiff base moieties have found a unique position during the *in vitro* and *in vivo* experiments for drug development against a huge number of biological entities including bacteria, fungi, cancer cells, viruses, parasites, etc.

**Keywords:** synthesis, isomerization, electronic and vibrational spectra, catalyst, antitumor

## 1. Introduction

Even Hugo Schiff might not know while publishing his research findings as a scientific communication some 155 years ago that these organic compounds would become an independent area of immense interest not only in chemistry but also in other areas of scientific domains including physical, materials, biological, and engineering [1, 2]. Simply, Schiff bases can be defined as the products of chemical reaction of a primary amine with an aldehyde or a ketone under a given set of conditions. Structurally, oxygen of the carbonyl functionality (C=O) in an aldehyde and/or a ketone is replaced with nitrogen leading to the formation of imine or azomethine or anilino or azimethine (C=N) functionality with the liberation of a water molecule which is characteristic of Schiff bases [3]. There has been a substantial increase to study the coordination of the Schiff bases to the transition metals as well as main group metals and main group organometallics. The aforementioned metallic derivatives of Schiff bases have shown a rich diversity of structural motifs based upon coordinating ability of the ligand under investigation [4–7].

Schiff bases and their metallic derivatives have got outstanding applicability in biological systems acting as antibacterial, antifungal, antiviral, antitubercular,

antitumor, insecticidal, bacteriostatic, in vitro cytotoxic, anti-inflammatory, analgesic, and antipyretic agents [8–15].

On the other hand, abiological applications of Schiff bases and their metallic derivatives are also very diverse, for example, in polymer chemistry, mechanochemical treatment often leads to the destruction of polymer under investigation, while very recently, the concept of mechanochemical polymerization has seen remarkable improvements which was initially reported with limited success [16]. Schiff base reaction is responsible for visual process in animals; the process starts with excitation of retinaldehyde leading to the formation of Schiff linkage with lysine and change in the membrane electrical potential with eventual transmission of signal to brain [17]. Schiff bases have been exploited very efficiently to monitor hazardous materials in the environment; for example,  $\text{Cr}^{3+}$  and organophosphates in the environmental samples were recognized, quantified, and removed with high accuracy and precision [18]. Electroanalytical techniques are very helpful for studying laboratory, clinical, and environmental samples as these are versatile and economical; Schiff bases have been known as ionophores and when fabricated with organic polymers can be transformed into membranes as ion-selective potentiometric sensors [19]. Schiff base ZnO complexes have been investigated as semiconductors by fabricating field-effect transistors to electronic performance [20]. Azo dye-based Schiff bases have been reported efficient chemosensors for detection and quantification of  $\text{S}^{2-}$  ions [21]. Photovoltaic characteristics of pyridine Schiff bases have been reported by illumination-dependent current–voltage measurements in solar cell applications [22]. Nickel Schiff base complexes have been studied for molecular docking experiments and their interaction with  $\beta$ -lactamase [23]. Schiff bases have successfully employed in vitro as well as in vivo for probing real-time sensing and analysis of  $\text{Al}^{3+}$  in a variety of diseases in human beings [24]. Polymeric Schiff bases strongly influence the electrochemical properties of the fuel cells and subsequent modification leading to an improved maximum power density in comparison to standard materials [25]. Metal–organic coordination polymers are widely used as conducting/semiconducting materials because of their accessible band gap 1–5 eV [26]. Schiff base palladium complexes immobilized on the mesoporous materials have been used as a heterogeneous catalyst for the Heck-Mizoroki coupling reaction and exhibited excellent catalytic activities for a wide range of alkenes [27, 28]. Schiff bases derived from cyclohexanediamine exhibited unusual structures, and these chiral molecules exhibited interesting photoluminescent properties [29].

## **2. Synthesis of Schiff bases and derivatives**

The following routes are commonly adopted to prepare Schiff bases and their metallic derivatives:

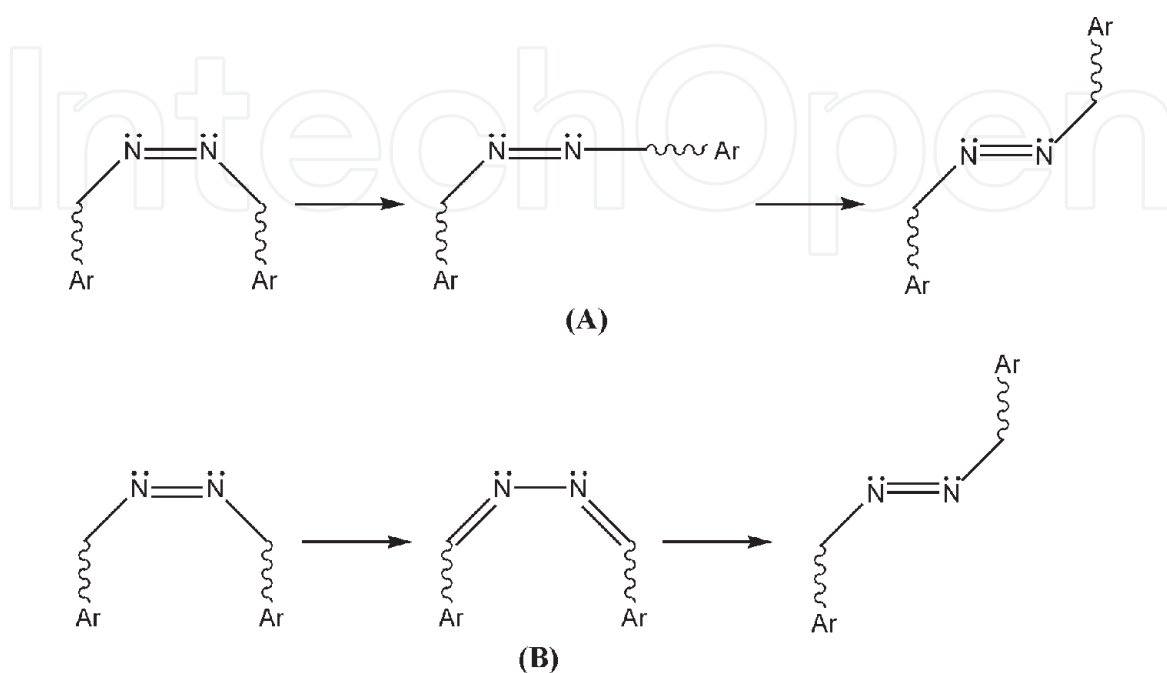
- Reaction of aldehydes/ketones with primary amines under acidic/basic conditions [30]
- Aldol-like condensation of aldehyde [31]
- Oxidative synthesis of imines from alcohols and amines [32]
- Addition of organometallic reagents to cyanides [33]
- Reaction of phenols and phenol-ethers with nitriles [34]
- Reaction of metal amides [35]
- Synthesis of ketimines from ketals [36]

- Reaction of olefins and tertiary alcohols with hydrazoic acid [37]
- Conversion of  $\alpha$ -amino acids into imines [38]
- Reduction of nitro compounds [39]

## 2.1 Isomerization of Schiff bases

Schiff bases tend to isomerize because of the imine group (C=N) to yield two stereoisomers *E* and *Z* (or *cis* and *trans*) isomers, and the formation of these stereoisomers can be controlled either kinetically or thermodynamically. Azobenzenes—common organic dyes—have been studied extensively owing to their potential applications in materials, medical, molecular switches, and other devices. Azobenzenes are photosensitive materials which undergo rapid reverse photoisomerization from the more stable *E* isomer to the less stable *Z* isomer. The exact mechanism of the *cis-trans* isomerization is not clear yet even after several decades of research. Reverse photoisomerization largely depends on the synthetic conditions like polarity of the medium; viscosity of the solvent used; and molecular substitutions on the azobenzene skeleton as these have very dramatic effects on the spectra of the molecules and the kinetics of isomerization [40].

In the literature, two possible mechanisms can be seen for the reversible photoisomerization of azobenzenes. First, the “inversion mechanism” (**Figure 1A**), proceeds via a linear transition state in which the N=N double bond remains undamaged, whereas the “rotation mechanism” (**Figure 1B**) occurs via a twisted transition state in which the N=N  $\pi$ -bond is broken. Extending the discussion, the *trans* form gets photoexcited, and an electron is excited from its ground state  $S_0$  orbital to its first or second singlet-excited state  $S_1$  or  $S_2$ , retaining its spin under an  $n-\pi^*$  or a  $\pi-\pi^*$  excitation, respectively. Azo groups (N=N) photoisomerize via two distinct mechanisms: the  $\pi-\pi^*$  transition with an out-of-plane rotation mechanism in which the N=N  $\pi$  bond is ruptured heterolytically or the  $n-\pi^*$  electronic transition with an inversion of one  $sp^2$  hybridized nitrogen atom through a  $sp$  hybridized linear transition state in which the double bond is retained. The rate of inversion isomerization is relatively



**Figure 1.**  
Mechanisms of photoisomerization of azobenzenes.

rapid and mostly independent of the medium's polarity or the nature of substituents on the azobenzene, but the rate for the rotation mechanism increases rapidly with increasing solvent polarity. During the photochemical studies of the unique properties of azobenzenes, considering the polarity of solvent effect of six different solvents, namely, cyclohexane, toluene, benzene, tetrahydrofuran, acetone, and 3-pentanol, on the kinetics of the *cis-trans* isomerization of 4-anilino-4'-nitroazobenzene using a camera flash and a UV-Vis spectrophotometer. The data obtained revealed that the rate of *cis-trans* interconversion is solvent dependent, while solvent polarity has no effect on the rate of isomerization going through inversion mechanism. This strong relationship between rate of reactions and polarity of solvent pointed to an intermediate transition state that is considerably more polar than the *cis* conformation. The increase in polarity of solvent resulted in an obvious decrease in the activation energy, entropy, enthalpy, and Gibbs free energy of activation for the *cis-trans* isomerization process, while structural changes and nature of substituents also played an important role in the isomerization mechanisms of azobenzenes [41].

More recently, thermal *cis-trans* isomerization with detailed spectral and kinetic data of 4-aminoazobenzene has been examined in a range of solvents of with varying polarities. Interestingly, unlike azobenzene, the rate of thermal isomerization of 4-aminoazobenzene is highly dependent on solvent polarity with marked increase in rates in polarity of solvents when compared to nonpolar solvents. Moreover, inversion is the preferred pathway in *cis-trans* thermal isomerization in a nonpolar medium; but, under polar conditions, the isomerization adopted a rotational behavior. The same study concluded that kinetics and the mechanism of thermal isomerization is controlled by the polarity of the medium [42–44].

Recently, effect of fluorine atom as substituent at either side of the double bond has also been thoroughly examined in a thermodynamic and kinetic perspective of *cis-trans* isomerization reactions. The work also comprehensively explained *cis effect* produced by *cis*-oriented fluorine atoms on opposite ends of the double bond. This substitution resulted in the fluorine-*cis* (*Z*) isomer being lower in energy than the *trans* contrary to conventional wisdom, in which steric interaction between *cis* substituents lead to *trans* isomer lower in energy. The following is a summary of the results. For  $\text{CF}_3\text{CF}=\text{CHF}$ , the enthalpy of isomerization was measured from the equilibrium constant data as a function of temperature, and it was observed that the *Z* (*cis*) isomer was of lower energy than the *E* (*trans*) isomer, and “*cis effect*” of fluorine was very pronounced. In another case, *E* (*trans*) isomer was lower in energy than the *Z* (*cis*) because of the destabilizing steric interaction of the two relatively large groups. The measurement of the steric interaction between the  $\text{CF}_3$  groups in the case of  $\text{Z-CF}_3\text{CH}=\text{CHCF}_3$  allowed a better interpretation of the measured *E*(*trans*) to *Z*(*cis*) enthalpy of isomerization than that already reported for  $\text{CF}_3\text{CF}=\text{CFCF}_3$ . The absolute rate constant of 2-butene's *cis* to *trans* isomerization is also reported; the activation energies of the *E* isomers when compared with that of *E*-2-butene showed that the uncoupling energy of the  $\pi$ -bond decreased with fluorine substitution across the double bond [45].

### 3. Spectroscopic properties of Schiff bases

UV-Visible spectroscopy is a very useful analytical tool for studying the spectral properties of Schiff bases generally obtained as mixture of geometrical isomers, their sensitivity to the solvent properties, effect of substitution, pH, ambient temperature, etc. Absorbance spectra are generally recorded in the range of 300–450 nm; and the spectra are strongly solvent dependent and the corresponding *E* or *Z* isomer. With isatin Schiff bases under consideration, *Z*(*cis*) isomer appeared at higher wavelengths, that is, of lower energy when compared with *E*(*trans*) at

lower wavelengths (higher energy); solvent-dependent electron density transfer was also observed, and the role of the position of substituent affected the appearance of frequency bands. Excited state was stabilized with a directional  $\pi$ -conjugative electron density shift in the molecule which might be a consequence of the long-range transmission of substituent effects, which supports the larger polarization of carbonyl group and thereby enhancing H-bonding capability of carbonyl oxygen and separation of electronic charges. Solvent affects are very complex phenomena, and the absorbance maxima altered inconsistently with respect to solvent and the position/type of the substituent(s) and geometrical features. In addition, other molecular properties like dipole moments, difference of electronegativity, partial charges, and chemical reactivity also significantly affected electronic spectra [46]. In the IR spectra, C=N is most commonly reported in the 1690–1640  $\text{cm}^{-1}$  region as a strong and a sharp band at somewhat lower frequencies than the bands of C=O groups and close to C=C stretching frequencies. Angle strain, steric repulsion, and other complicated local factors and solution concentration and nature of solvent, in neutral solvents, the stretching frequency of C=N is found to be at 1670  $\text{cm}^{-1}$ , and the corresponding force constant, 10.6 dynes  $\text{cm}^{-1}$ , is in the harmonic oscillator approximation. The frequency is usually lowered in the absence of one or more groups in conjugation with the C=N. Generally, there is no difference between IR and Raman frequencies and between the spectra of pure liquids and solids and their solutions in common organic solvents  $\text{CCl}_4$  or other not very associative solvents. Generally, water of crystallization appeared at 3300  $\text{cm}^{-1}$  plus range [46].

Multinuclear ( $^1\text{H}$  and  $^{13}\text{C}$ ) and multidimensional (HSQC, HMBC, COSY, and NOESY) NMR spectral analyses are helpful to establish absolute configuration of isatin Schiff bases. For example, the chemical shifts were assigned by a combined use of 1-D ( $^1\text{H}$  and  $^{13}\text{C}$  proton-decoupled and 2-D NMR experiments COSY, NOESY, HSQC, and HMBC). 2-D NOESY experiments were used to assess solution conformation of Schiff bases; *E* (*trans*) stereochemistry was assigned as major isomer in  $\text{DMSO-d}_6$  solutions. Signals of some protons considerably shifted upfield by approximately 1 ppm relative to the same signals in the parent isatin; in contrast, chemical shifts of the protons present in *Z* (*cis*) isomer showed no difference to those found in parent isatin. Similarly, the same analogy was applied to understand the electronic influences of substituents like  $-\text{NO}_2$ , and  $-\text{OH}$  and  $-\text{OCH}_3$  group showed only the presence of *E* (*trans*) isomer. In contrast, electron-donating groups enhanced the stability of *Z* (*cis*) isomer; these factors affected the physico-chemical properties and lead to the differences in biological behaviors because of varying isomeric compositions [47].

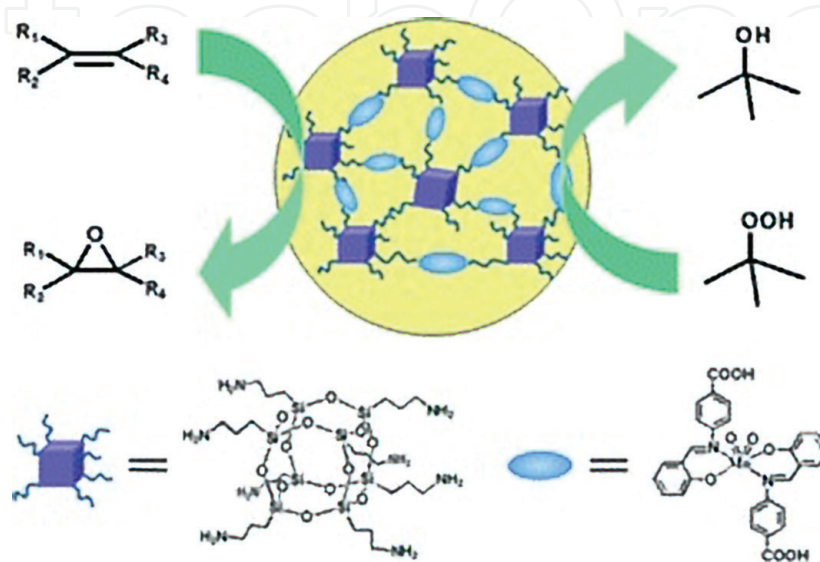
Generally, in physical sciences and especially in chemistry, hydrogen bonding is one of the very important concepts for the deciding properties of the new materials. Intramolecular hydrogen bonds in ortho-hydroxyaryl Schiff bases, in ortho-hydroxyaryl ketones and amides, and in proton sponges and related compounds could be considered as classical objects for the investigation. The geometric and spectroscopic characteristics of the H-bonds that are typical for H-bonds are of medium strength, that is, it is shortened XY contact, elongated XH, directionality trend, change in frequency, and shielding and de-shielding. One of the most prominent aspects is the possibility of delocalization of proton leading to tautomers; and the existence of tautomer's equilibrium depends on room temperature, nature of solvent, and substitution. Proton delocalization is also observed due to the formation of stronger intramolecular H-bonds with larger proton potentials and due to thermally fluctuating media; either of these phenomena cause influence on the geometry of H-bond. Tautomeric equilibria changed with the change in the intrinsic geometry and spectroscopic properties of contributing tautomers, which further complicated the analysis of the experimental data. Computational work often provides the necessary insight via adiabatic and nonadiabatic PES calculations; and

lastly, stabilization is also achieved due to delocalization of electrons in the chelate systems which are defined as resonance-assisted hydrogen bonds (RAHB) [48].

#### 4. Schiff base metallic derivatives as catalysts

Schiff bases are easily supported on polymers and loaded with different metallic ions to check their catalytic action; and these polymer-supported catalysts are consistent in drastic reaction conditions like moisture and high temperature reactions. A careful survey of literature reveals that during the past two decades, several reports were seen on the synthesis of polymer-supported Schiff base complexes catalysts.

Transition metal Schiff base complexes are well-recognized homogeneous catalysts for various organic transformations with high homogeneity, good reproducibility, selectivity, and excellent catalytic activity to catalyze reactions under routine conditions. But there are certain drawbacks associated with these catalysts like corrosion, contamination of products, and separation of the catalysts. To address these challenges, heterogeneous catalysis is a good alternative approach; and there are two steps to achieve this task, that is, dispersing metallic ions on porous solid supports categorized as solid supported liquid phase catalyst (SLPC), and second step is the easy separation of the supported species from reaction mixture by filtration. Polystyrene is a well worked out cost-effective support, easily available, mechanically robust, chemically inert, and facile functionalization. When compared with the other supports like alumina or silica, the polymer-supported catalysts furnish the polymer chain flexibility for better microenvironment. Cobalt Schiff base complexes-functionalized polystyrene were effective and excellent catalysts in resolution of racemic mixtures. For the epoxidation of alkenes, early transition metal complexes proved excellent catalysts in combination  $\text{H}_2\text{O}_2$ ; similarly, vanadium Schiff base complexes have been considered as versatile catalyst for oxidation of olefins, allylic alcohols, aromatic compounds, sulfides, and alcohols. There has always been a great need for high-quality pharmaceuticals, insecticides, and perfumes which significantly lead to develop enantioselective catalysts for epoxidation of olefins (**Figure 2**). More recently, chirally modified Li and Mg *t*-butyl peroxides have been used successfully in the epoxidation of electron deficient olefins. Henry's reaction also known as nitroaldol reaction is carbon-carbon



**Figure 2.** Epoxidation of olefin using a polyhedral oligomeric silsesquioxane (POSS)-bridged oxo-molybdenum Schiff base complex [49–51].

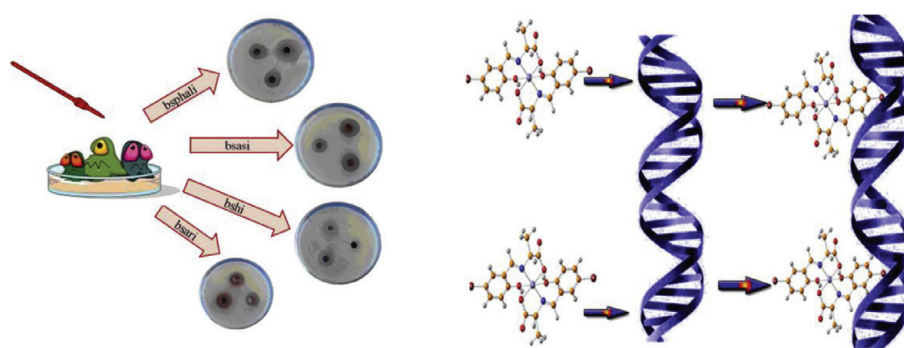
bond coupling of carbonyl groups and nitro alkanes to generate organic intermediate natural products, drugs, and dyes. Schiff base Cu complex exhibited a very high enantioselectivity but limited to 2-nitrobenzaldehyde; also, Cu complexes of iminopyridines catalyzed reactions of nitromethane with aliphatic and aromatic aldehydes. Cu complexes of salen Schiff bases improved the chiral induction of Henry's reaction (yield: 95%); the m- and p-substituted benzaldehydes required lower temperatures and inert conditions [49–51].

## 5. Biological significance of Schiff bases and their metallic derivatives

The progress of biological inorganic chemistry has seen a marked interest in Schiff base complexes, as many of these complexes may be considered as models for biologically important species. Co, Ni, Fe, Zn, and UO<sub>2</sub> Schiff base complexes of 2-thiophene displayed good antibacterial activity against *E. coli*, *P. aeruginosa*, and *S. pyogenes*; these complexes also inhibited the growth of Gram-positive bacterial strains *S. pyogenes* and *P. aeruginosa*. This unique property could be applied safely in the treatment of infections caused by any of these strains [52].

Platinum complexes of salicylaldehyde and 2-furaldehyde Schiff base with o- and p-phenylenediamine were screened against *E. coli*, *B. subtilis*, *P. aeruginosa*, and *S. aureus*; the data proved the complexes were more potent than the parent Schiff bases. Complexes of Schiff bases derived from sulfametrole and varelaldehyde were screened against *E. coli* and *S. aureus*, and it was observed to have a significant effect on *E. coli*. Membrane of Gram-negative bacteria contains lipopolysaccharides; the reported Schiff bases and their metallic complexes could combine with these lipophilic layers to enhance the membrane permeability of the Gram-negative bacteria. Lipophilicity is an important factor that controls the antibacterial activity as lipophilic cell membrane favored the passage of only lipid soluble materials; and this increase in lipophilic nature enhances the penetration of Schiff bases and their metallic complexes into the lipid membranes and seizing the growth of the organism. Schiff bases and their metallic derivatives are more toxic on *S. aureus* than on *E. coli*; it may be due to the SOH, OCH<sub>3</sub>, and CH<sub>3</sub>CH<sub>2</sub>CH groups, interacting with the lipophilic membrane (**Figure 3**) [53–55].

Cu, Ni, and Co complexes of 3-(2-hydroxy-3-ethoxybenzylideneamino)-5-methyl isoxazole and 3-(2-hydroxy-5-nitrobenzylidene amino)-5-methyl isoxazole Schiff bases were screened against *Aspergillus niger* and *Rhizoctonia solani*, and it was found that the activity increased upon coordination. The enhanced antifungal activity of the metal chelates can be explained based on chelation theory, which considers the overlapping of orbitals of each metallic ion with the ligand orbitals. Increased activity results in enhancement in the lipophilicities of the complexes due to delocalization of



**Figure 3.**  
Antibacterial activity and DNA interaction of Schiff bases [54, 55].



$\pi$ -electrons in the chelate ring; it is also reported that increased lipophilicity leads to breakdown of the permeability barrier of the cell. Cu complexes proved to be more active, which may be attributed to higher stability constant than the other complexes [56–58].

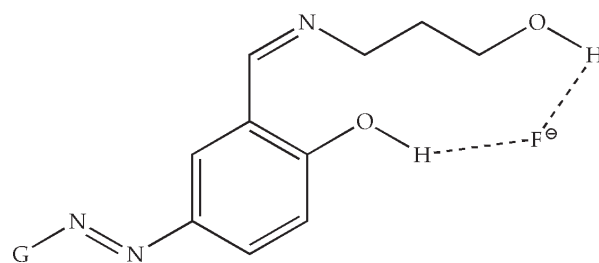
Schiff base metal complexes conjugated with oligonucleotides were used to inhibit antitumor effect; zinc fingers are small protein motifs consisting of finger-like projections with a  $Zn^{2+}$  ion in each lump typically coordinated to two histidines and two cysteinic moieties. Binding with DNA takes place via classical ( $C_2H_2$ )-type zinc finger which regulates metathesis making these exciting targets for cancer therapy, especially breast, lung, liver, and brain cancers. The transition metal ions coordinated to Schiff bases have a very high affinity toward amino acid residues such as histidine and cysteine; their interaction with Zn fingers can, therefore, result in displacing  $Zn^{2+}$  from the Zn-finger and prohibiting the DNA binding with transcription factor.  $Co^{3+}$  Schiff base complexes were also attempted and showed greater specificity toward transcription factor inhibition than either of the precursors, that is, oligonucleotide and/or  $Co^{3+}$  complex, and  $Co^{3+}$  complex was required in >100-fold concentration for transcription factor inhibition, and the interaction with the protein was also non-specific [59–63].

Vaccination is a preemptive strategy to counter viral attacks like polio, small pox, chicken pox, etc. Viral attacks are a life-threatening situation for patients with compromised immunity, and a prompt treatment is required. To counter this, therapeutic options for viral infections are limited as antiviral agents in clinical practice are not yet completely effective, due to viral mutation against the drugs, and in addition, they also present several side effects. 1-amino-3-hydroxyguanidine salicylaldehyde Schiff bases are being considered as a good platform for the design of new and effective antiviral agents against mouse hepatitis with 50% growth inhibition at very low concentrations. Recently, abacavir-derived series of new Schiff bases prodrugs have been reported to use to treat human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) under the trade name Ziagen (GlaxoSmithKline) [64].

Recently, researchers have focused work in search of metal-based antioxidants to identify the compounds having the potential in scavenging free radicals relevant to diseases associated with oxidative damage caused by reactive oxygen species. Synthetic antioxidants are widely used as effective and low-cost than natural antioxidants. Schiff base metallic derivatives have been reported as effective scavengers of reactive oxygen species acting as antioxidants [65].

## **6. Schiff base sensors**

Sensor may be defined as system capable of detecting changes in its surroundings and transferring the information obtained to computer processor. During the past two decades, researchers have shown an increasing interest to develop new molecules/materials for the sensing of chemical species present in the environment. For example, inorganic anions and cations have a very huge impact on biological systems and the environment; these ions affect a wide range of chemical and biological processes in terms of toxicity to environment as well as human health. All the discussed points account for the aforesaid growth in the demand for ion-selective sensors. Anion sensors development is a very challenging task in comparison to cations as anions are larger in size, geometrically very diverse, and more importantly pH dependent. Chemosensors are abiotic molecules which have the selective and reversible binding ability with the analyte; azo Schiff bases have been reported as fluoride chemosensors. On the hand, Schiff base fluorescent sensors are becoming



**Figure 4.**  
Fluoride ion sensing by Schiff bases [66].

first choice as they exhibit high sensitivity even at very low concentration of analyte under consideration. In analytical chemistry, electrochemical methods are based on two fundamental parts, namely, *receptor*, and second is *transducer*, either performing transformation of the chemical information. The first does it into a form of energy, and second transforms the chemical information into a useful signal, respectively. Recently, azo Schiff bases chemosensors have been studied to show high selectivity and sensitivity for the detection of  $\text{Hg}^{2+}$ ,  $\text{Cd}^{2+}$ , and fluoride ions in the presence of competing cations/anions; these chemosensors can be utilized in DMSO by both selective coloration and change in the absorption spectra with a more prominent color change that is observable to the naked eye (**Figure 4**) [66, 67].

## 7. Schiff base energy applications

Energy demand is a daunting challenge confronting the world as the quality of life depends largely on the availability of energy as we have burnt major part of fossil fuels. Renewable energy sources like solar light and wind generate larger amounts of energy and could potentially solve our immediate energy demands. Transformation of light into electric power in photovoltaic cells and subsequently light generation are two important interconnected phenomena which focus considerable interest to the researchers. Schiff base  $\text{Zn}^{2+}$  and  $\text{Pt}^{2+}$  complexes and organometallic compounds can produce, transform, and utilize energy due to their unique electronic setup which can be easily modified varying their chemical structure to develop a suitable material to fit an energy application. Remarkable work has been reported on salicylaldimine Schiff bases complexes with divalent Cu, Ni, Co, Zn, Mn, Fe, and Pt capable of being tailored into materials of applications in photo-physics and optoelectronics [68].

### Conflict of interest

The corresponding author on behalf of all the co-authors exclusively declares that there is/are no conflict(s) of interest(s) among authors to be declared.

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