International Journal of Multidisciplinary Science and Innovation (IJMSI)
Website: https://ijmsi.in/
ISSN: 3107-5754
Vol. 2, Issue 1, Jan-Jun, 2026
Page No.: 196-202

Research

Synthesis and Pharmacological Activities of Schiff Base Derivatives: An Overview

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DOI: *10.62896/ijmsi.2.1.22*

Conflict of interest: *NIL*

Article History
Received: 08/02/2026
Accepted: 10/05/2026
Published: 13/05/2026

Abstract:
Schiff bases are an important class of organic compounds characterized by the presence of an azomethine group (–C=N–), generally synthesized by condensation reactions between primary amines and aldehydes or ketones. Due to their structural diversity, ease of synthesis, and remarkable pharmacological properties, Schiff base derivatives have emerged as promising candidates in medicinal chemistry and pharmaceutical research. The present review highlights recent advances in the synthesis, physicochemical characteristics, metal complex formation, and pharmacological activities of Schiff base derivatives. Various synthetic approaches including conventional heating, microwave-assisted synthesis, solvent-free synthesis, and green chemistry methods have been discussed. Schiff bases and their metal complexes exhibit broad-spectrum biological activities such as antimicrobial, antifungal, antiviral, anti-inflammatory, antioxidant, anticonvulsant, antitubercular, antidepressant, antidiabetic, antihypertensive, and anticancer activities. Their ability to chelate transition metal ions significantly enhances their biological potential and therapeutic applications. The review also focuses on structure–activity relationship studies, mechanisms of action, analytical characterization techniques, and future perspectives for the development of novel Schiff base derivatives as therapeutic agents. Owing to their excellent pharmacological profile and synthetic versatility, Schiff bases continue to attract substantial attention in modern drug discovery and development research.

Keywords: Schiff bases, azomethines, medicinal chemistry, antimicrobial activity, anticancer activity, metal complexes, pharmacological activity, synthesis, hydrazones.

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1. INTRODUCTION

A Schiff base, named after Hugo Schiff, is a compound with a functional group that contains a carbon-nitrogen double bond with the nitrogen atom connected to an aryl or alkyl group, not hydrogen. Schiff bases, in a broad sense, have the general formula R1R2C=NR3, where R is an organic side chain. In this definition, Schiff base is synonymous with azomethines. Some restrict the term to the secondary aldimines (azomethines where the carbon is connected to a hydrogen atom), thus with the general formula RCH=NR'. The chain on the nitrogen makes the Schiff base stable imines. A Schiff base derived from aniline, where R3 is a phenyl or a substituted phenyl. Schiff bases are formed when any primary amine reacts with an aldehyde or a ketone under specific conditions. Structurally, a Schiff base (also known as an imines or azomethine) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (C=O) has been replaced by an imine or azomethine group. Schiff bases are some of the most widely used organic compounds. We also highlight the most significant examples of compounds belonging to this class that exhibit analgesic, anti-inflammatory, antimicrobial, and non-ulcerogenic activities reported in the literature [1].

Schiff bases are crystalline or oily substances that are insoluble in water and soluble in organic solvents. They are weak bases, forming salts with acids in an anhydrous medium; in aqueous acid solutions, they undergo hydrolysis to yield an amine and aldehyde. The majority of Schiff bases are stable in alkaline solutions. Schiff bases are valuable intermediate products of organic synthesis, for example, in the preparation of secondary amines and various heterocyclic compounds. The Schiff bases known as azomethines dyes are used for dyeing acetate and synthetic fibers; they are also used in color photography to reduce the photosensitivity of photographic emulsions. Schiff base metal complexes have been studied extensively because of their attractive chemical and physical properties and their wide range of applications in numerous scientific areas. These types of complexes have been vigorously explored in recent years and such studies have been the subject of many papers and reviews. Many of them are centered on the catalytic activity of Schiff base complexes in a large number of homogeneous and heterogeneous reactions.

1.1 CHEMISTRY OF SCHIFF BASE

Schiff bases are synthesized by the reaction of an aldehyde or ketone with a primary amine in the presence of a dehydrating agent. The reaction mechanism involves the formation of an imine intermediate, which is then converted to the final Schiff base product by the elimination of water. The reaction is usually catalyzed by an acid or a base, depending on the nature of the starting materials. Schiff bases can also be prepared by the reaction of an amine with a carbonyl compound in the presence of a Lewis acid catalyst.

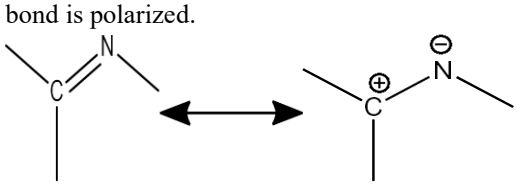
One of the most important properties of Schiff bases is their ability to coordinate with metal ions, forming metal complexes that have various applications in catalysis, sensing, and materials science. The imine nitrogen atom in Schiff bases can act as a donor ligand, forming a coordination bond with the metal ion. The coordination chemistry of Schiff bases has been extensively studied, and various metal complexes have been synthesized with different geometries and electronic properties.

The applications of Schiff bases in various fields are numerous. In medicine, Schiff bases have been used as antimicrobial agents, anticancer agents, and enzyme inhibitors. In materials science, Schiff bases have been used as photochromic dyes, fluorescent probes, and catalysts. In analytical chemistry, Schiff bases have been used as colourimetric and fluorescent probes for the detection of metal ions and biomolecules.

Schiff bases are versatile compounds that exhibit unique properties, such as their ability to coordinate with metal ions, exhibit photochromism, and act as fluorescent probes.

1.2 PHYSICAL PROPERTIES OF SCHIFF BASES

Schiff bases are often solids that are colored and transparent. Due to their exact melting points, they are used to quantify metal concentrations and identify carbonyl compounds Because the carbon-nitrogen double bond in Schiff bases spins more easily than the carbon-carbon double bond, stereoisomers can trans form in to one another. Because nitrogen has a higher electro negative charge than carbon, the azomethine bond is polarized.



In general, the isolation of stereoisomers of Schiff bases is challenging due to their relatively

small energy differences. However, exceptions exist. When the nitrogen atom is hindered by an electronegative group, the rotation around the azomethine bond becomes restricted, allowing for the separation of stereoisomers. The presence of an electronegative group on the azomethine group pushes the negative charges on the nitrogen atom towards the carbon, resulting in a decrease in polarization and an enhancement of the covalent double bond character. This contributes to the stability and distinct properties of the stereoisomers.

Due to the nitrogen atom's unshared electron pairs and the double bond's capacity to donate electrons, compounds with an azomethine group exhibit fundamental properties. However, compared to their equivalent amines, Schiff bases typically show worse basicity. This is a result of the nitrogen atom's transition from sp3 hybridization in amines to sp2 hybridization in the imine structure of Schiff bases.

The increase in the s character of the hybrid orbital as a result of sp2 hybridization leads to a decrease in basicity. The higher s character reduces the availability of the lone pair of electrons on the nitrogen atom for donation, resulting in diminished basic characteristics of Schiff bases compared to amines. The C-N system in Schiff bases shows absorption in the UV region, although it is considered a weak chromophore. Conjugation with phenyl groups shifts the absorption to the visible spectrum, resulting in a shorter wavelength of absorption. Additionally, the presence of deactivating substituents, like halogens, on the attached aromatic ring can further influence the absorption properties, causing a decrease in the absorption wavelength.

In the infrared (IR) spectrum, the C-N bond stretching vibrations in Schiff bases are typically observed in the range of 1610-1635 cm-1. However, if the C-N bond is positively charged, the IR stretch bands are shifted to higher frequencies, typically observed at 1665-1690 cm-1. These spectral characteristics provide valuable information about the structural features and bonding nature of Schiff bases.

Overall, the absorption and IR properties of Schiff bases are influenced by the conjugation of the C-N system with aromatic groups, the presence of electron-donating or electron-withdrawing substituents, and the nature of the C-N bond itself.

1.3 CHEMICAL PROPERTIES OF SCHIFF BASES

The characteristics of Schiff bases are influenced by the substituents attached to the azomethine (C=N) group. When the nitrogen atom is connected to an electronegative group, the stability of the Schiff base molecule increases.

This is best exemplified by the fact that Schiff bases with alkyl or aryl substituent on the nitrogen atom are more prone to hydrolysis compared to oximes with hydroxyl group so the nitrogen atom, as well as phenyl hydrazones and semicarbazones with NH groups. While Schiff bases exhibit resistance to alkaline conditions, they undergo hydrolysis in an acidic environment, breaking down into amine and carbonyl compounds. This hydrolysis reaction is facilitated by the protonation of the nitrogen atom, which makes it more susceptible to nucleophilic attack by water, leading to the cleavage of the C=N bond. Therefore, the stability and susceptibility to hydrolysis of Schiff bases are influenced by the nature of the substituents attached to the nitrogen atom of the azomethine group.

Reversibility is an inherent characteristic of the Schiff base formation reaction. The reaction involves the condensation of an aldehyde or ketone with an amine, resulting in the formation of a Schiff base and the release of one mole of water. The presence of water in the surroundings can drive the equilibrium of the reaction to the left, favouring the hydrolysis of the Schiff base back into its starting components [2].

Furthermore, the choice of amines with electronegative atoms and unpaired electrons, such as aromatic amines, can also enhance the efficiency of Schiff base formation. The presence of the electron-donating substituents on the nitrogen atom stabilizes the Schiff base and makes it less prone to hydrolysis. This allows for the separation and isolation of Schiff bases with a high degree of efficiency, as hydrolysis is minimized. By carefully controlling the reaction conditions, including solvent choice and reactant selection, the reversibility and hydrolysis of Schiff bases can be effectively managed, leading to efficient synthesis and isolation of the desired products.

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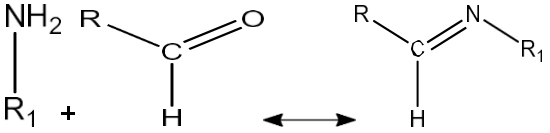
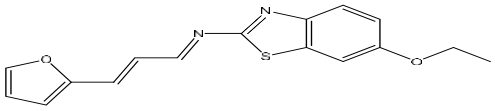


1.4 BIOLOGICAL ACTIVITY SCHIFF BASE

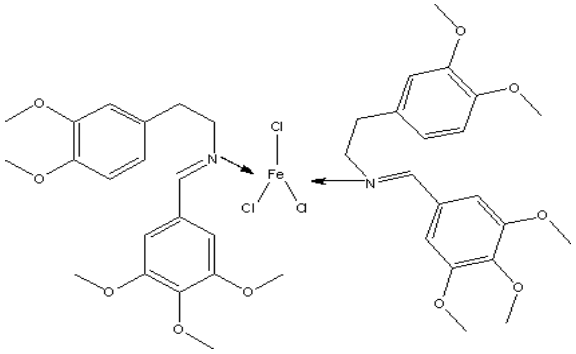
A variety of biological activity, including antibacterial, antiviral, anticancer, anti-inflammatory, and antioxidant characteristics, have been linked to schiff bases. The existence of functional groups that may interact with biological molecules through hydrogen bonds, electrostatic interactions, and covalent bonds is thought to be the cause of the Schiff bases' biological activity. The presence of a conjugated system in Schiff bases also contributes to their biological activity by enabling electron transfer and free radical scavenging.

One of the most significant biological functions of Schiff bases is antimicrobial activity. It has been demonstrated that Schiff bases have antibacterial action against a variety of pathogens, such as bacteria, fungus, and viruses. The antimicrobial activity of Schiff bases is due to their ability to disrupt the cell membrane or cell wall of microorganisms, resulting in cell death. Schiff bases also inhibit the activity of enzymes involved in the biosynthesis of essential molecules, such as DNA, RNA, and proteins, leading to the inhibition of microbial growth. Another important biological activity of Schiff bases is their anticancer activity. Schiff bases have been shown to exhibit cytotoxicity against various cancer cell lines, including breast, lung, colon, and prostate cancer. Because they can cause cancer cells to undergo apoptosis (programmed cell death), suppress cell growth, and mess with the cell cycle, Schiff bases have anticancer properties. The activity of enzymes involved in the metabolism and signal transmission of cancer cells can also be inhibited by schiff bases, which will stop the proliferation of cancer cells. Additionally, it has been demonstrated that schiff bases have antiviral properties against a variety of viruses, including as the influenza virus, herpes simplex virus, and HIV. The antiviral activity of Schiff bases is due to their ability to interfere with the viral life cycle, inhibit viral replication, and block viral entry into host cells. Schiff bases can also activate the immune system, leading to the clearance of viral infections. In addition to their antimicrobial, anticancer, and antiviral activities, Schiff bases exhibit antioxidant and anti-inflammatory properties. Schiff bases can scavenge free radicals and inhibit oxidative stress, leading to the prevention of cellular damage. Schiff bases can also inhibit the production of pro-inflammatory cytokines, leading to the inhibition of inflammation [3].

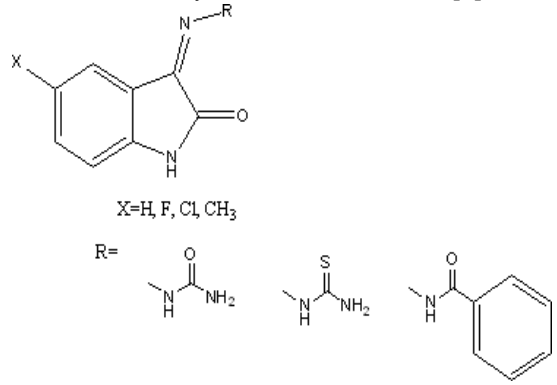
The new Schiff base According to Abu-Yamin, this compound is N-(6-ethoxybenzo[d]thiazol-2-yl)- 3-(furan-2-yl)prop-2-en-1-imine. Screening was done on the Schiff base and its complexes to look for things like antibacterial, antifungal, antioxidant, and anticancer activity.



Schiff bases were used in the work published by Nureen et al, and their iron and zinc metal complexes were synthesised. Several spectroscopic methods, including Ultraviolet-visible spectroscopy (UV-Vis), Fourier-transform infrared spectroscopy (FTIR), Nuclear magnetic resonance spectroscopy (NMR), and Mass spectrometry (MS), were used to characterize the ligands and their metal complexes.



The synthesis and characterization of Schiff base compounds produced from 5-substituted isatins and bioactive amines/hydrazides were the main objectives of the 2016 study by Tehrani et al. The objective was to investigate these chemicals' possible bioactivity. Spectroscopic methods, such as nuclear magnetic resonance, infrared spectroscopy, and mass spectrometry, were used to confirm the structures of the synthesized Schiff bases [6].



2. PHARMACOLOGICAL ACTIVITIES OF SCHIFF BASES

2.1 Antimicrobial Activity

Schiff base derivatives exhibit potent antibacterial and antifungal activities against a wide range of Gram-positive and Gram-negative microorganisms. The antimicrobial activity of these compounds is primarily attributed to the presence of the azomethine (–C=N–) group, which interferes with microbial enzyme systems and disrupts the integrity of the cell membrane, ultimately leading to microbial cell death. Several Schiff base derivatives have demonstrated significant activity against pathogenic microorganisms such as *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans*, and *Pseudomonas aeruginosa*. Moreover, the antimicrobial efficacy of Schiff bases is often enhanced after complexation with transition metal ions, as metal complexes improve lipophilicity, facilitate penetration through microbial cell membranes, and strengthen interactions with biological targets. These findings indicate that Schiff base derivatives and their metal complexes hold great potential as promising antimicrobial agents for combating resistant microbial infections[7].

2.2Antitubercular Activity

Many Schiff bases have demonstrated inhibitory effects against *Mycobacterium tuberculosis*. Their lipophilic nature facilitates penetration into the mycobacterial cell wall.

Hydrazone-based Schiff bases are especially effective as antitubercular agents.

2.3 Anticancer Activity

Schiff base derivatives possess remarkable anticancer properties due to their ability to induce apoptosis and inhibit the proliferation of tumor cells. Numerous Schiff base compounds have demonstrated significant cytotoxic activity against various cancer cell lines including breast cancer, colon cancer, lung cancer, prostate cancer, and leukemia. The anticancer activity of Schiff bases is mainly attributed to multiple mechanisms such as DNA intercalation, inhibition of essential cellular enzymes, generation of reactive oxygen species, and arrest of the cell cycle, ultimately leading to programmed cell death. Furthermore, the formation of metal complexes with Schiff bases has been reported to enhance their anticancer potential by increasing cellular permeability, improving bioavailability, and facilitating stronger interactions with biological targets. These findings suggest that Schiff base derivatives and their metal complexes represent promising candidates for the development of novel anticancer agents in modern medicinal chemistry.

2.4 Anti-inflammatory Activity

Schiff bases inhibit inflammatory mediators such as prostaglandins and cytokines. Many derivatives exhibit comparable activity to standard NSAIDs with reduced gastrointestinal toxicity.

2.5 Antioxidant Activity

The conjugated system of Schiff bases contributes to free radical scavenging activity. Schiff bases neutralize reactive oxygen species and reduce oxidative stress.

2.6 Antiviral Activity

Several Schiff base derivatives have demonstrated significant antiviral properties against a variety of pathogenic viruses including Herpes simplex virus (HSV), Influenza virus, and Human Immunodeficiency Virus (HIV). The antiviral activity of these compounds is primarily attributed to their ability to inhibit viral replication and interfere with essential viral enzymes involved in the viral life cycle. Schiff bases may also prevent viral entry into host cells and disrupt nucleic acid synthesis, thereby reducing viral proliferation. Furthermore, the presence of electron-donating and electron-withdrawing substituents in Schiff base derivatives can enhance their antiviral potency and selectivity. Due to these promising antiviral mechanisms, Schiff base compounds are considered potential candidates for the development of novel antiviral therapeutic agents.

2.7 Anticonvulsant Activity

Schiff bases containing heterocyclic rings exhibit anticonvulsant properties by modulating neurotransmitter systems in the central nervous system.

2.8 Antidepressant and Anxiolytic Activity

Recent investigations have reported Schiff base derivatives possessing antidepressant and anxiolytic activities through modulation of monoaminergic neurotransmission and antioxidant mechanisms.

2.9 Antidiabetic Activity

Certain Schiff bases inhibit carbohydrate metabolizing enzymes such as α-amylase and α-glucosidase, thereby exhibiting antidiabetic potential.

3. FUTURE PERSPECTIVES

Schiff base derivatives continue to attract considerable attention in medicinal chemistry due to their diverse pharmacological activities and structural versatility. Future research in this field is expected to focus on the development of novel Schiff base compounds with improved selectivity, enhanced therapeutic efficacy, and reduced toxicity. Advanced synthetic approaches such as microwave-assisted synthesis, green chemistry techniques, nanotechnology-based formulations, and computational drug design may significantly contribute to the discovery of more potent derivatives. The incorporation of Schiff bases into metal complexes and nano-carrier systems can further enhance bioavailability and target specificity. In addition, molecular docking, QSAR studies, and artificial intelligence-based drug discovery approaches may help in identifying lead molecules with better pharmacokinetic and pharmacodynamic profiles. Schiff base derivatives also hold promise in the treatment of multidrug-resistant microbial infections, cancer, neurodegenerative disorders, and inflammatory diseases. Therefore, continuous exploration of Schiff base chemistry may provide new opportunities for the development of safer and more effective therapeutic agents in modern pharmaceutical research [8].

CONCLUSION

Schiff bases represent a highly versatile and biologically important class of compounds with immense applications in medicinal chemistry and pharmaceutical sciences. Their easy synthesis, structural diversity, and broad spectrum of pharmacological activities make them promising candidates for drug discovery and therapeutic development. Schiff base derivatives and their metal complexes have demonstrated remarkable antimicrobial, anticancer, anti-inflammatory, antioxidant, antiviral, anticonvulsant, and antitubercular properties. The azomethine linkage plays a critical role in biological interactions and pharmacological efficacy. Continued research involving green synthetic methodologies, structure–activity relationship studies, computational modeling, and metal complexation may lead to the development of safer and more effective therapeutic agents in the future. Schiff bases therefore remain a valuable pharmacophore in modern medicinal chemistry research.

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