Chapter

Schiff Base as Multifaceted Bioactive Core

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Abstract

Schiff bases are the condensation products of primary amines and carbonyl compounds, which are becoming more and more significant. Schiff bases are imine or azomethine (–C=N–) functional group containing compounds that are produced through a nucleophile addition process. Excellent chelators called Schiff bases have a place in both qualitative and quantitative analysis of metals in aqueous media. Schiff bases were discovered to be auxiliary scaffolds and adaptable pharmacophore for the creation and production of numerous bioactive leads compounds, and this special quality made them accessible for a wide range of biological applications. Schiff bases exhibit significant biological properties including analgesic, anti-inflammatory, antibacterial, anticonvulsant, anti-tubercular, anticancer, antioxidant, anthelmintic antiglycation, and antidepressant activities. In situ cross-linked hydrogel systems are created using the Schiff bases, which are frequently utilized in coordination, organometallic chemistry, and tissue engineering applications. The role of Schiff bases to the design and creation of new lead with potential biological functions is highlighted in this chapter. Researchers' interest in obtaining the most conclusive and suggestive information on the numerous Schiff bases that have been important for therapeutic purposes over the last few decades and their use in coordination complexes has been maintained by this bioactive core.

Keywords: Schiff bases, azomethine, pharmacophore, coordination complexes, biological

1. Introduction

Schiff bases derivatives are novel approaches to researchers for designing heterocyclic/aryl compounds for emergence of new-fangled nature-friendly technology [1]. Schiff bases have been employed as synthons in the generation of various industrial and biological active compounds such as formazans, 4-thiazolidines, benzoxazines, and so on, namely ring closure, cycloaddition, and replacement reactions [2]. It has played an important role in the development of coordination chemistry and was included as key point in the progression of inorganic biochemistry and optical materials [3].

Basically, Schiff bases are the novel approach compounds that possess imine or azomethine (–C=N–) functional group. Hugo Schiff et al. had first reported that Schiff bases are the condensed product of primary amines and carbonyl compounds [4–7]. In coordination chemistry, Schiff bases are most important class of the widely used organic compounds and have widely application in several fields including inorganic, biological, and analytical chemistry. Schiff bases are important in the therapeutic purposes in medicinal and pharmaceutical field due to its broadly biological activity such as analgesic [8–10], anti-inflammatory [11], anticancer [12, 13], antioxidant [14], anthelmintic [15], antimicrobial [16, 17], anticonvulsant [18], antitubercular [19], and so on. The presence of N atom of azomethine that involved to form of H-bond with active residue of the protein in the cell and influences cellular mechanisms [20, 21]. Moreover, Schiff bases also play an intermediately role in synthesis of organic compounds, pigments, dyes, polymer stabilizers [7], and for corrosion inhibitors [22]. However, studies revealed that metal complexes of Schiff bases depict more biological activity than free organic compounds [23]. Abdel-Rahman et al. [24] have testified numerous transition metal complexes of Schiff bases as ligands that must be different biological activities, likewise antifungal, anticancer, antibacterial, and so on. As example, Fe (II) complexes have been designed, developed, and synthesized using different Schiff bases ligands that derived from 5- bromosalicylaldehyde and variety of alpha-amino acids such as L-arginine, L-histidine, L-phenylalanine, L-aspartic acid, and L-alanine. Although, these complexes are tested for their antimicrobial activity against various bacterial species such as Escherichia coli, Pseudomonas aeruginosa, and Bacillus cereus. Therefore, it is found that Fe (II) complexes unveiled strong antibacterial activities as compared with amino acid Schiff bases ligands. Moreover, Fe (II) complexes were well interacted with calf thymus DNA using UV-visible spectroscopy, and agarose gel electrophoresis measurement at pH = 7.2. As a result, these complexes showed constant binding with different DNA [25]. However, complexes of Schiff base ligand 2-[(2-Hydroxy-3-methoxy-benzylidene)-amino]pyridin- 3-ol obtained from 2-amino-3-hydroxy-pyridine and 3- methoxysalicylaldehyde with nanosized Fe(II), Cd(II), and Zn(II) metals have been synthesized by sonication method, and all complexes examined for antimicrobial activity against various bacterial species [26]. Recent study revealed that some metal complexes of Schiff bases have greater cytotoxic activity against colon cancerous cell (HCT-116 cell line). Since the middle of the nineteenth century, metal Schiff base complexes have been recognized. Their usage as Schiff base ligands, which are typically monodentate, bidentate, tridentate, tetradentate, etc., and depend on the presence of donor atoms, has been noted in a significant amount of literature. Because they can create stable compounds with transition metals, they are widely used in coordination chemistry [27].

Researchers have focused their research on the chemistry of metal Schiff base complexes with nitrogen and other donor atoms because of their numerous applications in dyes, polymers, enzyme preparation, as well as used as catalyst in various biological systems. This is due to the stability of Schiff base metal complexes as well as biological activity [28], electrochemistry [29], and potential applications in oxidation catalysis [30]. Due to their selectivity, sensitivity, and synthetic flexibility to the central metal atom and the presence of an azomethine group, which aids in elucidating the biological transformation reaction's mechanism, Schiff bases are widely investigated [31].

Some Cu (II), Co (II), and Ni (II) complexes have been described employing Schiff base ligands generated from 2-amino-3-hydroxypyridine and 3-methoxysalicylaldehyde, and their in vitro antibacterial properties against many bacteria and fungi have been examined. These complexes were further examined for DNA binding, and it was discovered that they could attach to DNA in an intercalative way. However, when compared with the clinically used vinblastine standard, the cytotoxicity of these metal Schiff base complexes on different cell lines such as human colon carcinoma cells (HCT-116 cell line) and breast carcinoma cells (MCF-7 cell line) demonstrated effective cytotoxicity against the growth of carcinoma cells [32]. Che et al. [33] stated that complexes of Pt (II) with Schiff base ligands N,N0-bis(salicylidene)-1,2-ethylenediamine (L1), N,N0- bis(salicylidene)-1,3-propanediamine (L2), and N,N0-bis(salicylidene)- 1,1,2,2-tetramethylethylenediamine (L3) revealed the use of vapor-deposited Pt (II)-salen (11) triplet emitters as for efficient electrophosphorescent dyes in multilayer organic light-emitting diode (OLED) devices with a maximum luminous efficiency of 31 Cd A^{-1}. They discovered that the performance of OLEDs utilizing the Schiff base dopant L3 outperforms that of previously reported Pt (II) emitters.

The majority of Schiff bases are created by condensing salicylaldehyde with both aliphatic and aromatic amines. By using the condensation process of salicylaldehyde with substituted anilines and other aromatic amines, Calvin and Bailes [34] described a number of imines.

These compounds' intriguing electronic characteristics were discovered through spectroscopic research. According to reports, the existence of a lone pair of electrons in these compounds may explain why there is a stronger ligation with metal ions. In the most recent years, several such azomethines and their complexes with various transition metals have been recorded in review papers [35, 36].

Similarly, Gao and Zheung [37] synthesized Schiff base ligands by condensation of 2-hydroxyacetophenone with various chiral diamines such as 1,2-diamino-cyclohexane, 1,2-diphenylethylenediamine, and 2,20-diamino- 1,10-binaphthalene, respectively, to investigate the steric, electronic, and geometric effect of a methyl (-CH3) group on an azomethine carbon in asymmetric catalytic reaction. Because of the impact of p-conjugation in such luminous complexes, More et al. [37] identified Ni (II) and Zn (II) salophen complexes as potential nonlinear optical materials. A considerable number of Schiff base metal complexes have been shown to be relatively good biological compound models [38].

Schiff bases have played an important part in the advancement of contemporary coordination chemistry, as well as in the advancement of inorganic biochemistry, catalysis, and valuable materials due to optical and magnetic characteristics [39]. In recent years, light emission or charge transport capacity technology has piqued the interest of electronic devices such as solar cells and active components for image and data treatment storage [40]. Metal complexes of Schiff bases contain distinct metals (paramagnetic) groups ascribed to magnetism [41].

2. Synthetic approach for Schiff base

Any primary amine can react with an aldehyde or a ketone under appropriate circumstances to produce Schiff bases. Hugo Schiff (1834–1915), a great chemist who was honored by having Schiff base named in his honor, was born in Frankfurt/Main, Germany's thriving Jewish community. The Schiff base generally has the following common structure (**Figure 1**). A Schiff base is a nitrogen analog of an aldehyde or ketone in which the carbonyl group (CO) has been replaced by an imine or azomethine group. It is also known as an imine or an azomethine [42].

The library of organic chemistry has a number of amines and carbonyl compounds that make it possible to create Schiff bases with a variety of structural characteristics.

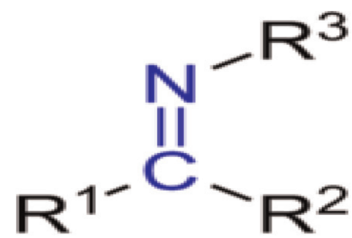


Figure 1.
General structure of Schiff Base (R^1 and R^2 both would be hydrogens. Alkyl or aryl members made up R^3.) [https://en.wikipedia.org/wiki/Schiff_base].

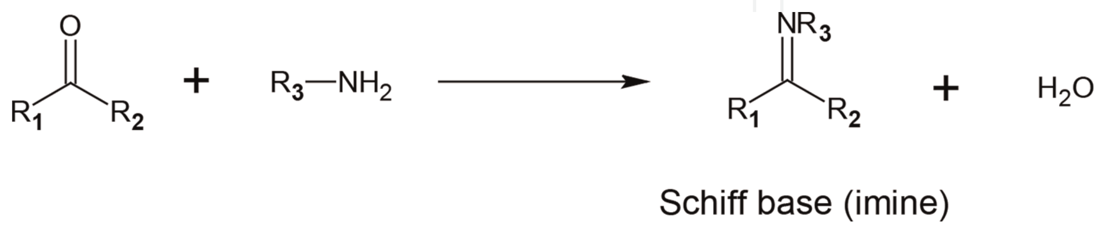


Figure 2.
Schiff base formation reaction scheme [45].

The basic carbonyl group for the production of Schiff bases can be an aldehyde (aromatic or aliphatic) or a ketone [43, 44]. The presence of substituent groups connected to the (>C=N) linkage regulates the stability of the imine group. The general reaction for the synthesis of the Schiff base is shown in (**Figure 2**) where R denotes an alkyl, aryl, cycloalkyl, or heterocyclic group, which might be variably substituted, and R1 may be an alkyl, aryl group, or H atom [46]. Refluxing the mixture under neutral conditions or with acid or basic catalysts usually causes the Schiff base to develop, which is a reversible process. Usually, the product separation or water removal is what brings the formation to completion [47].

Schiff bases are still synthesized by chemists, and today, active and well-designed Schiff base ligands are referred to as "privileged ligands." The bridging Schiff's bases have the following structure, which has a variety of functional groups that can be altered to suit different needs. R" is phenyl or a substituted phenyl, H is an alkyl or aryl group, and X is a phenyl or substituted phenyl group. In fact, Schiff bases have the ability to stable a wide range of metals in a variety of oxidation states, regulating the performance of metals in a wide range of advantageous catalytic transformations. The oxygen atoms in Schiff bases can be changed to sulfur, nitrogen, or selenium atoms; however, NO or N_2O_2-donor groups are the most frequent donor groups [48].

The mechanism of forming a Schiff base (**Figure 3**) is an additional application of the nucleophilic addition to the carbonyl group. The amine is the nucleophile in this situation. The amine interacts with the aldehyde or ketone in the first step of the process to produce carbinolamine, an unstable addition product. By bases or acids catalyzing the process, the carbinolamine loses water. The dehydration of the carbinolamine is acid-catalyzed because it is an alcohol. The reaction is typically catalyzed by acids because the dehydration of the carbinolamine is the rate-determining step in the production of the Schiff base. However, because amines are basic molecules, the acid concentration cannot be too high. The equilibrium is pulled to the left, and carbinolamine production is prevented if the amine is protonated and turns non-nucleophilic. As a result, low acidity is preferred for many Schiff base

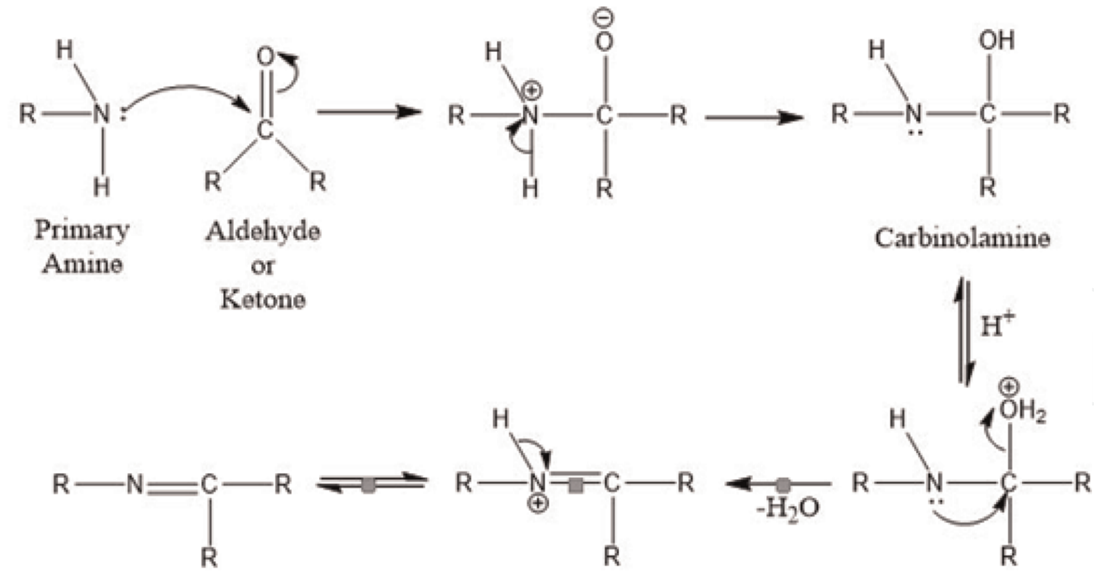


Figure 3.
Mechanism of Schiff base formation [48].

synthess. Base can also catalyze the dehydration of carbinolamines. Despite not being a concerted reaction, this reaction is somewhat comparable to the E2 elimination of alkyl halides. Through an anionic intermediate, it moves forward in two steps. The process of creating a Schiff base actually involves two different types of reactions, addition and elimination [48, 49].

In the meantime, a number of methods and systems for the synthesis of Schiff base have been described, including $NaHCO_3$ [44], $CuSO_4$ [46], P_2O_5/Al_2O_3 [47], $MgClO_4$ [45], $ZnCl_2$ [50], and $MgSO_4$-PPTS [51]. In these systems, metal species act as Lewis acids to activate the carbonyl group and facilitate the removal of water. A few developments have been reported in recent years due to the advancement of experimental procedures, such as solid-state synthesis [52], solvent-free/clay/microwave irradiation [53], water suspension medium [54], reflux/solvent [55], infrared irradiation/no solvent [56], and K-10/microwave. The mentioned methods/systems revealed some drawbacks, including the need for high reaction temperatures, prolonged reaction times, and moisture-sensitive catalysts, huge amounts of aromatic solvents, expensive dehydrating reagents/catalysts, and specialized equipment [57]. $NaHSO_4.SiO_2$/microwave/solvent-free [58], dirhodium caprolactamate [59], [bmim] BF_4/molecular sieves [60], silica/ultrasound irradiation [61], silica/microwave [19], and silica/solvent-free [62].

Conventional Method for synthesis of Schiff Base: In order to make Schiff bases, aldehyde (0.004 mol) and different aromatic amines (2a–e) (0.004 mol) were condensed in water (10 ml) and agitated at room temperature. TLC has taken note of the reaction's progression. After the reaction was complete, a yellow-color, amorphous product was left behind. This product was filtered, dried, and then recrystallized from methanol [48].

Microwave synthesis for Schiff Base: A mixture of aldehyde (0.004 mol) and substituted aromatic amines (0.004 mol) in water (1 ml) was added and microwaved at 200 W for 30–60 seconds. TLC made note of how the reaction was progressing. Following the completion of the reaction, the reaction mixture contained a solid product, which was filtered and recondensed with methanol [48].

3. Spectroscopic analysis of Schiff base

A Schiff base is a compound with the general structure $R_1R_2C{=}NR'$. They can be considered a subclass of imines, which is also synonymous with azomethine [63]. In order to investigate hybrid composites, spectroscopic analysis is used. The analysis reveals useful details such as elemental type, chemical composition, optical and electronic properties, and crystallinity. Ultraviolet and visible light (UV-vis) spectroscopy, elemental analysis, differential scanning calorimetric (DSC), hydrogen nuclear magnetic resonance (1H NMR), and Fourier transform infrared (FTIR) studies are used to evaluate these Schiff bases [64].

In the IR spectra, C=N is most commonly reported in the 1690–1640 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. With angle strain, steric repulsion, other complicated local factors, solution concentration and nature of solvent, the stretching frequency of C=N is found to be at 1670 cm^{-1}. The frequency is usually lowered in the absence of one or more groups in conjugation with the C=N [65]. The multinuclear (^{1}H and ^{13}C) NMR spectral analyses are helpful to characterize and confirm the structure of Schiff bases. The upfield and downfield shifting of the signal is dependent upon the substituents present over the Schiff bases. In the CHN analysis of the Schiff bases, the elemental and sometimes isotopic compositions were found out for the confirmation of the structure of the synthesized derivatives.

It is important to note that the nitrogen atom in the Schiff base has a lone pair, which gives it the characteristics of a Lewis base and allows it to participate in the creation of hydrogen bonds, either intramolecularly or with polar molecules. This characteristic encourages the development of intramolecular hydrogen bonding, particularly when suitable non-polar solvents are present [66].

4. Schiff-base metal complexes

Schiff-base metal complexes have been considered the active topic of research in coordination chemistry during a few decades of extensive research on metal-based pharmaceuticals, owing to their useful applications in numerous disciplines of science. They have potential therapeutic applications as antibiotics, antimicrobials, antitumors, antivirals, anti-inflammatory medicines, analgesics, antifungals, and many others [47]. Schiff bases are versatile pharmacophores that trap in metal ions within their structural units due to the presence of multiple donor atoms [67]. Schiff bases (azomethines) are formed by combining amino and carbonyl groups with multidentate ligands and forming highly significant complexes with metal ions. By using azomethine nitrogen, they can coordinate with metal ions. In organic synthesis, the Schiff base reaction is fundamental for the synthesis of C-N bonds. (**Figure 4**) They exhibit chelation property with O, N, and S donors, and metal complexes have a diverse biological action against many infections and cancers. Schiff base complexes with multidentate ligands are capable of chelating any metal ions. These ligands are effective in the exciting unique therapeutic approach to better understanding diseases and their therapy. The complexes of Schiff base of both transition metal ions (i.e., inner and outer) containing NO or NOS donor atoms were described as playing a significant role in biological activities. Because they are colorful and very stable for biological activities, certain of these metal complexes have attractive physical and chemical properties [69]. Some of the recently synthesized Schiff-base metal complexes are enlisted in **Table 1**.

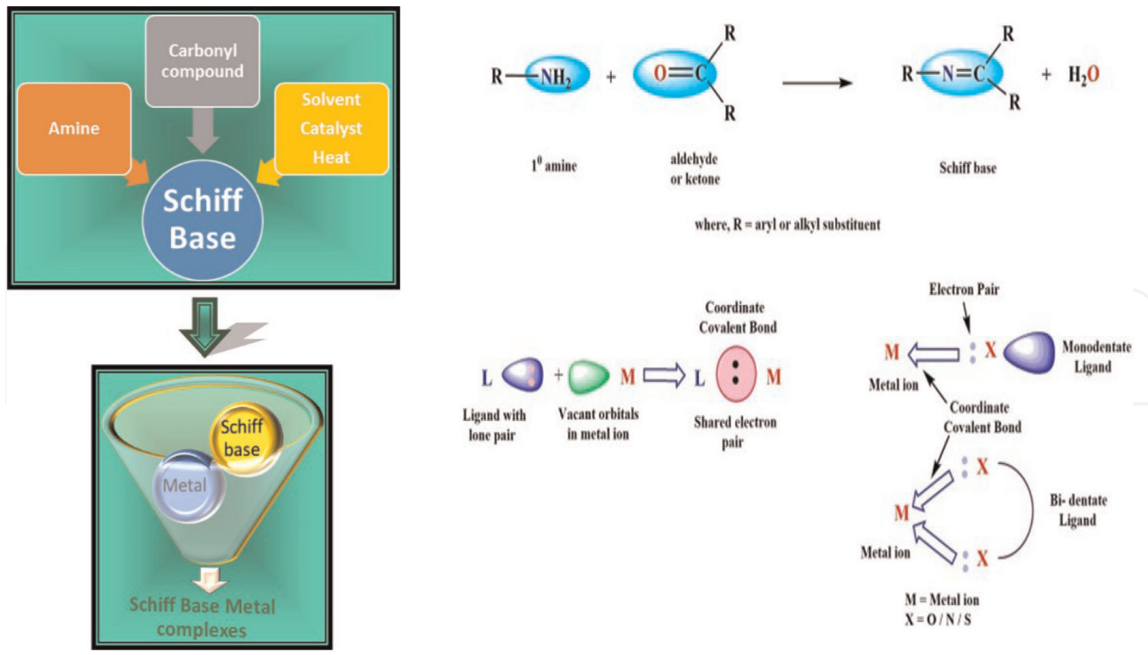


Figure 4.
Formation of Schiff-base metal complexes [68, 69].

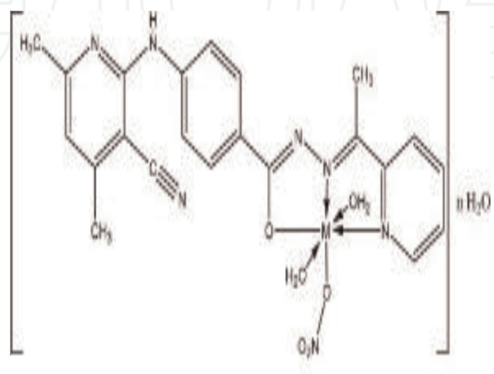
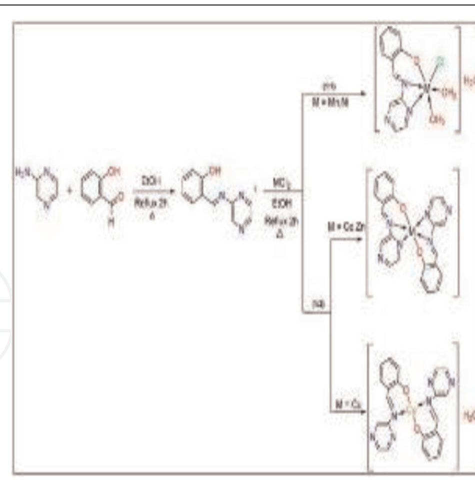
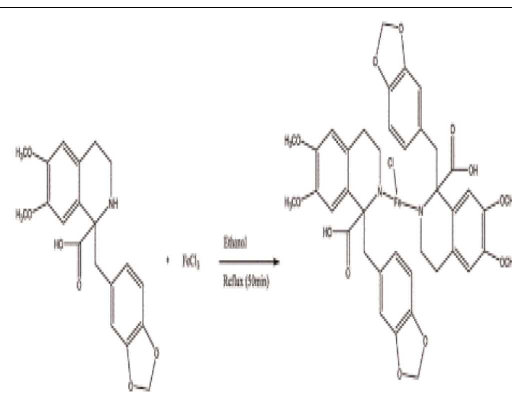
5. Schiff base biological activity

Bacteria that display multiple antibiotic resistance [77] are closely linked to the rise in the mortality rate of infectious illnesses [78]. The main reason for this issue is the lack of efficient therapies. There is unquestionably an urgent medical need for the creation of new antibacterial drugs with inventive and more effective modes of action. Hence, Schiff bases called azomethines containing nitrogenous analogue of carbonyl compound changed by imine group are used. For antimicrobial activity, these bases produce excellent activity [79]. Aside from natural and synthetic molecules, biomolecules, sulfonamides, coumarins, aminothiazolyl, bromocoumarins, O-phthaldehyde, or 2-aminophenol, and 1, 2, 4-triazoles are other molecules that can be used as platforms to create Schiff bases for antibacterial activities [80].

As malaria is a disorder associated with severe health problems of public and globally its cases are increasing. Hence, various authors synthesized antimalarial Schiff base derivatives for prominent activity [81]. Also these bases have maximum activity for fungal infection due to its structure. In case of viral disorder, in the market there are numbers of drugs, but they are not fully active due to mutations in viruses. To overcome these problems, Schiff base derivatives are synthesized as an antiviral agent [82]. Different biological activities of Schiff bases are shown in **Table 2**.

6. Schiffs base abiological activity

Schiff base possesses various medicinal activities. In addition to the same, they are now being used in diagnostics also. Some of the abioloical applications of Schiff's base are mentioned in this section.

Sr. no.	Schiff base metal complexes	Work done / Scheme	References
	Influence of co-ligand on the biological properties of Schiff base metal complexes: Synthesis, characterization, cytotoxicity, and antimicrobial studies.	In this work, six new mixed ligand Schiff base metal complexes of $[M_2(L^1)(X)_2Cl_4]$ type, (where, M = Co^{II}, Ni^{II}, Cu^{II}, L^1 = Schiff base ligand derived from 1-pyrenecarboxaldehyde and 1,4-bis[3-aminopropyl]piperazine and X = pyrazine-2-carboxylic acid or 2,2′-biimidazole) were synthesized	[70]
	Synthesis, characterization, design, molecular docking, anti COVID-19 activity, DFT calculations of novel Schiff base with some transition metal complexes	 M= Co(II) (n=4); Ni(II) (n=2); Cu(II) (n=0)	[71]
	Synthesis, molecular docking, molecular dynamic, quantum calculation, and antibacterial activity of new Schiff base-metal complexes	Synthesis of Schiff base compounds Ligands (L1 and L2) synthesized from the condensation of Nicotinic acid carbohydrazide with vanillin or 2-chloroquinoline-3-carbaldehyde. The transition metal Co(II) and Cu(II) afforded the Schiff base-metal complexes by metalation.	[72]
	Synthesis, Spectroscopic Characterization and Biological Studies of Mn(II), Cu(II), Ni(II), Co(II) and Zn(II) Complexes with New Schiff Base of 2-((Pyrazine-2-ylimino)methyl)phenol		[73]
	Iron (III) and Zinc (II) Metal Alkaloid Complexes: Synthesis, Characterization and Biological Activities		[74]

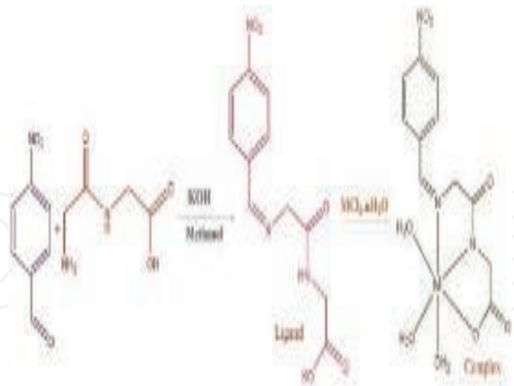
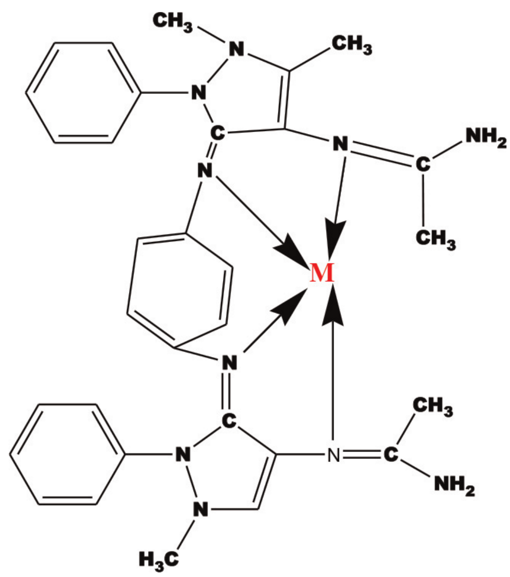
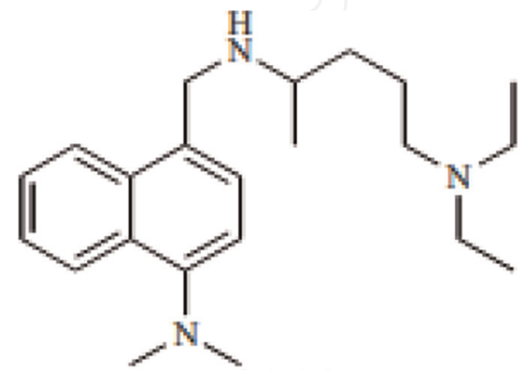
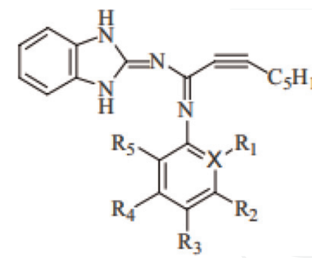
Sr. no.	Schiff base metal complexes	Work done / Scheme	References
	Novel water soluble Schiff base metal complexes: Synthesis, characterization, antimicrobial-, DNA cleavage, and anticancer activity		[75]
	Synthesis, characterization and biological studies of Schiff base metal complexes derived from 4-aminoantipyrine, acetamide and p-phenylenediamine		[76]

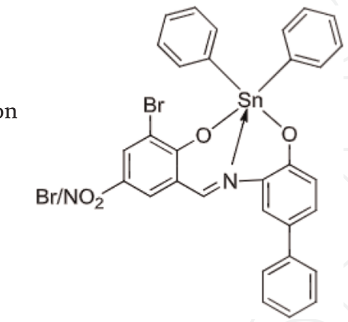
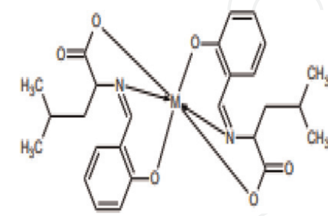
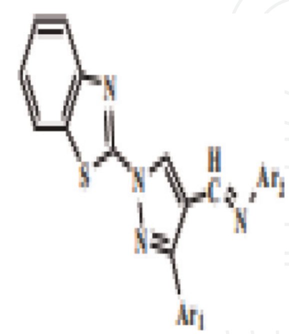
Table 1.
Recently synthesized Schiff-base metal complex.

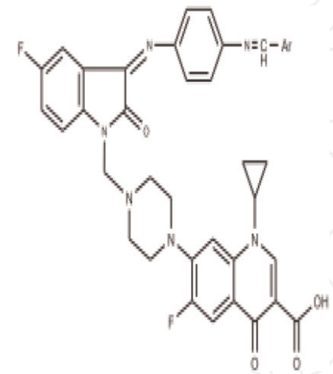
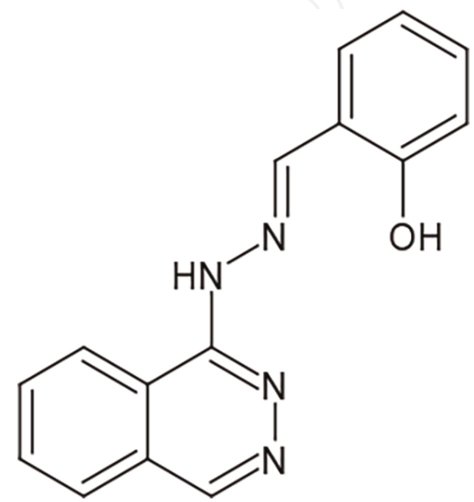
6.1 Bioimaging applications

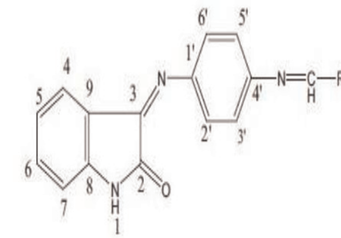
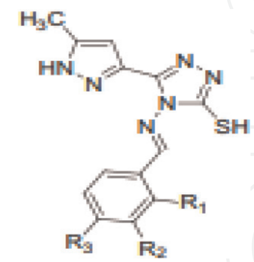
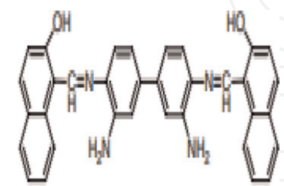
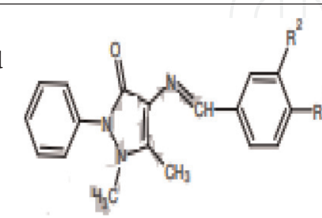
A variety of Schiff base probes with fluorescent sensors are used for bioimaging applications to detect metal ions. Most of the fluorescent probes selectively and sensitively detect only one or two metal ions. Schiff base probes detect analytes in non-aqueous or semi-aqueous media, making them useful for the detection and monitoring of toxic ions in drinking water and industrial waste [100]. A simple and versatile Schiff base chemical sensor was developed to detect four adjacent series 4 metal ions (Co2+, Ni2+, Cu2+, and Zn2+) by colorimetric or fluorometric methods. This chemical sensor has been used to image Zn2+ in HepG2 cells, zebrafish, and tumor-bearing mice, demonstrating potential biological applications [101]. The fluorescence sensor synthesized from the reaction of picolinohydrazide and 4 (diethylamino) salicylaldehyde successfully detected Al3+ and Zn2+ in living cells, suggesting that this simple biosensor has great potential for biological imaging applications [102].

Antimicrobial activity

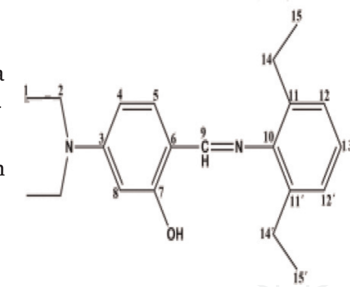
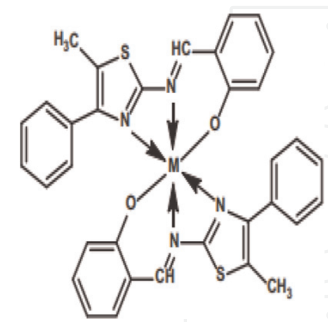
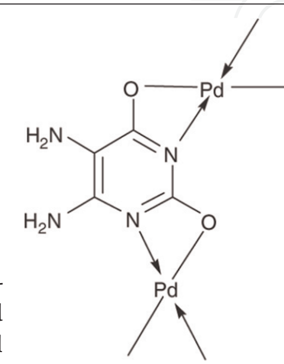
S.N.	Title	MIC/ IC_{50}	Work done	Structure	Ref
1	Synthesis, Characterization, and Antimalarial Activity of Novel Schiff Base-Phenol and Naphthalene-Amine Ligands	IC_{50} 1.7 micro M	Harpstrite *et al* synthesized Schiff base of phenol and naphthalene by using condensation reactions of 2-Amino-5-diethylamino-pentane and appropriately substituted benzaldehyde or naphthaldehyde in methanol and traerythrocytic culture was used for this acivity by the method of Trager and Jensen for antimicrobial activity CQ-resistant Dd2 strains		[83]
2	Benzimidazole Schiff base derivatives: synthesis, characterization and antimicrobial activity	MIC 125 μg/mL	Fonkui *et al* synthesized benzimidazole Schiff base derivatives for that Oct-2-ynoic acid (1,3-dihydrobenzoimidazole-2-ylidene)amide was used as starting material which was mixed with different derivatives of aniline in hot ethanol using broth micro dilution technique in which six Gram-positive and eight Gram-negative bacteria were used, authors performed different activity on synthesized derivative as antifungal by using different fungi and different ligands concentrations, anti-malarial and antiparasitic activity. From the synthesized derivatives those containing hydroxyl group, carboxyl group and sulfonyl group showed highest MIC.		[84]

Antimicrobial activity					
S.N.	**Title**	**MIC/ IC_{50}**	**Work done**	**Structure**	**Ref**
3	Synthesis, characterization, in vitro antimicrobial, antioxidant and anti-inflammatory activities of diorganotin (IV) complexes derived from salicylaldehyde Schiff bases	25 μg/mL	Devi *et al* synthesized Diorganotin (IV) with Schiff base as complexes were promising areas for antimicrobial activity in coordination chemistry. For MIC determination Serial dilution method was used. Synthesized derivative 20 shows highest MIC.		[85]
4	Synthesis, spectral and antimicrobial studies of amino acid derivative Schiff base metal (Co, Mn, Cu, and Cd) complexes	MIC 11.47 μg/ mL	Pervaiz *et al* synthesized leucine and salicyldehyde and were combined to create the amino acid derivative Schiff base in a basic media. Antimicrobial and antifungal activity were carried out by using standard Rifampicin and Fluconazole respectively. Mn (L) showed highest MIC as standard showed 21 μg/mL		[86]
5	Pyrazole Schiff base hybrids as anti-malarial agents: Synthesis, In vitro screening and computational study	EC50 (6bf) 1.95 μg/ml and (6bd) 1.98 μg/ml	Agrawal *et al* synthesized pyrazole Schiff base for that 2-hydrazinobenzothiazole was used as starting material. Antimalarial activity was done in vitro by using Schizont Maturation Inhibition method against P. falciparum by utilizing RPMI 1640 to grow in human A (+) red blood cells medium and AB (+) serum gentamycin sulfate. Among all derivatives 6bf and 6bd shows highest EC_{50} value having p -CH_3Ph group and meta and para -ClPh group		[87]

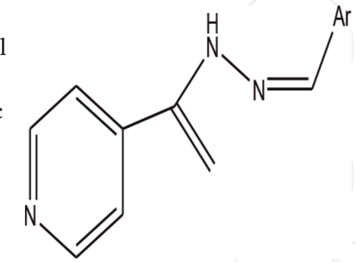
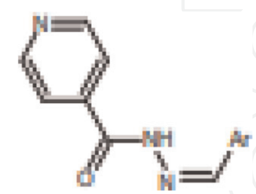
Antimicrobial activity					
S.N.	**Title**	**MIC/ IC_{50}**	**Work done**	**Structure**	**Ref**
6	Schiff Bases: A Versatile Pharmacophore		Prakash *et al* synthesized Schiff bases and mannish bases from 5-fluoro isatin for antimicrobial activity by cup plate method from that substituted with electron-donating group of 7-(4-((3-(4-(4Hydroxybenzylideneamino) phenylimino)-5-fluoro-2-oxindolin-1-yl) methyl) piperazin-1-yl)-1-cyclopr opyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (3c) compound shows highest MIC compared to Ciprofloxacin and Ketoconazole. Those derivatives having electron withdrawing effects like nitro and chloro group showed lesser inhibition.		[88]
7	Novel Hydralazine Schiff Base Derivatives and Their Antimicrobial, Antioxidant and Antiplasmodial Properties	MIC 31.25 μg/ ml	Sathe *et al* synthesized hydralazine Schiff base derivatives such as 3-[1-(2-(phthalazin-1-yl) hydrazono)ethyl]-1,3-oxa- zinane (PHEO) and 2-[(2-(phthalazin-1 yl) hydrazono) methyl] phenol (PHMP), from that only PHMP showed higher activity		[7]

Antimicrobial activity					
S.N.	**Title**	**MIC/ IC_{50}**	**Work done**	**Structure**	**Ref**
Other activities					
S.N	Title		Work done		
8	Synthesis, characterization, and analgesic activity of novel Schiff base of Isatin derivatives		Chinnasamy *et al* synthesized Isatin Schiff bases by using imesatin and different aromatic aldehydes. Analgesic activity was done by using tail immersion method by using swiss mice having 200 mg/kg body weight and standard drug used was pentazocin. From the synthesized derivatives compound having electron donating groups shows higher analgesic activity such as -(4-hydroxy-3-methoxybenzyllideneamino) phenylimino) indoline-2-one (5i) compound		[11]
9	Synthesis, antioxidant and analgesic activities of Schiff bases of 4-amino-1, 2, 4-triazole derivatives containing a pyrazole moiety		Karrouchi *et al* synthesized pyrazole Schiff base and by using Tail flick method analgesic activity was carried out using morphine as standard drug and for its evaluation g acetic acid induced writhing method with albino mice was used. In vitro antioxidant activity was carried out by using DPPH (2, 2-diphenyl-1-picrylhydrazyl) radical. 5 h derivatives having fluoro group showed better analgesic activity.		[89]
10	Synthesis, anti-inflammatory, analgesic and kinase (CDK-1, CDK-5 and GSK-3) inhibition activity evaluation of benzimidazole/ benzoxazole derivatives and some Schiff's bases		Sondhi *et al* synthesized Schiff base derivatives of benzimidazole and benzoxazole, anti-inflammatory activity was carried out in the carrageenin-induced paw oedema model in albino rats with 50 kg/mg. Chloro group containing derivatives shows higher activity, derivative naming 4, 4' bis [1-{(2-aminophenylimino) methyl] naphthalen-2-ol showed good anti-inflammatory activity.		[90]
11	Synthesis and biological evaluation of Schiff bases of 4-aminophenazone as an anti-inflammatory, analgesic and antipyretic agent		Murtaza *et al* synthesized 4-aminophenazone Schiff base, anti-inflammatory activity was done by Carrageenan-induced paw oedema method using albino mice with piroxicam as standard drug. Antipyretic studies was carried through Yeast induced hyper pyrexia (YIHP) in rabbits. Derivative 4-{[(4-bromophenyl)methylidene]amino}-1,5-dimethyl-2-phenyl-		[91]

Antimicrobial activity

S.N.	Title	MIC/ IC_{50}	Work done	Structure	Ref
			1,2-dihydro-3H-pyrazol-3-one (4APZAB) showed greater activity than others		
12	Synthesis, characterization, and anticancer activity of Schiff bases		Uddin N synthesized Schiff base by condensation reaction between benzaldehydes and amines in ethanol. Human cervical cancer cells HeLa and human breast adenocarcinoma cells MCF-7 were used in an MTT (dimethyl-2-thiazolyl-2, 5-diphenyl-2H-tetrazolium bromide) based cell viability assay to assess the derivatives potential for cytotoxicity Carboplatin as standard drug. Derivative L5 (5-(diethylamino)-2-((2,6 diethylphenylimino) methyl) phenol showed significant activity		[92]
13	Synthesis, anticancer activity and molecular docking study of Schiff base complexes containing thiazole moiety		Abd-Elzaher *et al* synthesized Schiff base by condensation reaction between salicylaldehydes and thiazole moiety. Different human tumor cell lines, including breast cancer MCF-7, liver cancer HepG2, lung carcinoma A549, and colorectal cancer HCT116, were demonstrated by synthetic Schiff base derivatives in contrast to the activity of doxorubicin as a reference medication.		[93]
14	Schiff Bases and their Metal Complexes as Potential Anticancer Candidates: A Review of Recent Works		Tadele *et al* reviewed Schiff base with metal complexes as anticancer agents includes activity as anti-HepG2 and anti-MCF-7 cell activity of quinazolines was extremely high. The strongest activity against various cancer cells was shown by [Ni (HL1)2(OAc) 2], among pyrazole-naphthalene derivatives. Azosal and its tin (IV) complexes shown outstanding efficacy against HCT-116 cell lines and significant activity against U-1242 MG. High activity was shown by 2-thiouracil sulfonamides against MCF7 and CaCo-2 cancer cells. In the presence of visible light, vitamin B6 and its oxovanadium complex shown good action against cervical cancer HeLa, MCF-7, and 3 T3 cell lines. High activity was		[94]

Antimicrobial activity

S.N.	Title	MIC/ IC_{50}	Work done	Structure	Ref
			shown by Indoles against AMJ13. While its binuclear (Y and K) complexes showed high activity against various cancer cells, porphyrine derivatives showed good action. The [Pd(II) and Pt(II)] chitosan complexes exhibited very significant anticancer activity against MCF-7 carcinoma cell.		
15	Schiff Bases: Interesting Scaffolds with Promising Antitumoral Properties		Iacopetta *et al* reviewed antitumor activity of synthesized Schiff base derivatives as mono Schiff derivatives were useful in leukemia cell line. 2, 4 dinitro substituted Schiff base against Human leukemia (HL-60). Also reviewed Potato disc tumor induction assay using Agrobacterium tumefaciens method for this ferrocene containing Schiff base showed highest inhibition of tumor growth. Surfactants used to fight colon cancer (HCT-116), breast cancer (MCF-7), and liver cancer (HepG2) cell lines all include Schiff bases with various lengths of hydrocarbon chains and from that C14 chain containing carbon showed highest inhibition. Anthracene-containing Schiff bases used in human epithelial cancer cell lines. For esophageal cancer cell lines an imine moiety bases were used. Phenylimino-1, 2-diphenylethanol derivatives were used in cell lines of human colon carcinoma and breast carcinoma. Pyranoquinolinone moiety containing Schiff bases used breast cancer cell lines.		[95]
16	Synthesis and biological evaluation of Schiff's bases and 2-azetidinones of isonocotinyl hydrazone as potential antidepressant and nootropic agents		Thomas *et al* synthesized Schiff bases by cyclocondensation reactions in microwave synthesizer. Synthesized derivatives were tested on swiss albino mice for nootropic activity by elevated plus maze test method. For antidepressant activity Forced swim test and tail suspension test in mice were carried out. Authors interpreted that the studied substances, including 2-azetidinones and Schiff's bases with electron-withdrawing (nitro, halogen, and dimethoxy) moiety on the phenyl ring, were found to have significant *in vivo* nootropic and antidepressant actions in the animal models.		[96]

Antimicrobial activity

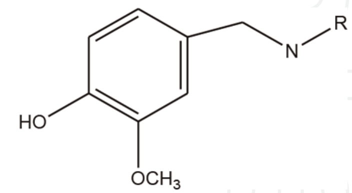
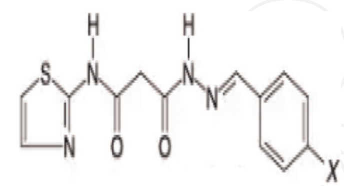
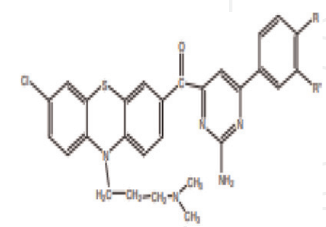
S.N.	Title	MIC/ IC_{50}	Work done	Structure	Ref
17	The Synthesis of Schiff bases and new secondary amine derivatives of p-vanillin and evaluation of their neuroprotective, antidiabetic, antidepressant and antioxidant potentials		*Yuldasheva et al* synthesized Schiff base derivatives of p-vanillin. Neuroprotective by using standard drug neostigmine and galantamine synthesized derivatives of p-vanillin with dopamine and with 4-aminomorpholine showing prominent activity. Acarbose as standard for antidiabetic and trolox for antioxidant activity for them p-vanilline with dopamine showed best among the other derivatives. That means this derivative was most potent inhibitors of glycosidase function.		[97]
18	Synthesis and reactions of thiosemicarbazides, triazoles, and Schiff bases as antihypertensive alpha-blocking agents		Authors prepared derivatives by condensing the hydrazide with aldehydes, 2, 3-pyridinedicarboxylic anhydride, or 1, 8-naphthalenedicarboxylic anhydride, Schiff bases were created. For testing white guinea pigs were used. It revealed that several of these chemicals have low toxicity and good hypertension –blocking efficacy.		[98]
19	Design, synthesis, spectroscopic characterization and anti-psychotic investigation of some novel Azo dye/Schiff base/Chalcone derivatives.		Gopi et al. synthesized azo, Schiff base and chalcone derivatives. Synthesize derivatives GC8 and GC2 has strong catalepsy induction potency carried out by catalepsy test and its score.		[99]

Table 2.
Different biological activities of Schiff bases.

Compound (E)-1-((L-glutaminoimino) methyl)naphthalene-2-ol (A) showed good solubility and compatibility in the presence or absence of Al3+ and showed some fluorescence in human Hs27 epithelial cells. Bioimaging has been reported [4]. Fluorescent Schiff base organotin dyes (1: Et2N-L-SnPh2, 2: Et2N-L-SnBu2, 3: MeO-L-SnPh2, 4: MeO-L-SnBu2, 5: HO-L-SnPh2, and 6: HO − L-SnBu2, L = 2-hydroxybenzylidene-4-hydroxybenzhydrazine) showed efficient two-photon excitation (1–4). Two of the compounds (5 and 6) were found to be able to selectively accumulate in HeLa cells, allowing their differentiation from normal cells (periodontal ligament cells) [103, 104].

6.2 Phosphorescent OLEDS

Five one-armed Schiff base ligands HL1, HL2, HL3, HL4, and HL5 were obtained from condensation of various group-substituted salicylaldehydes with aniline and 2,4,5-trifluoroaniline gave. Their platinum(II) complexes Pt(L1)2, Pt(L2)2, Pt(L3)2, Pt(L4)2, Pt(L5)2, and PtL5 DMSO obtained by the metalation of ligands with K2PtCl4 were found to be excellent candidates for phosphorescent OLEDs [105]. The luminescent performance of azomethine zinc complexes in organic light-emitting diodes has been investigated, and the results have shown excellent electroluminescence properties as blue fluorescent light sources [106]. Schiff-base zinc metal complexes have been developed to serve as efficient light-emitting materials for optoelectronic applications such as organic light-emitting diodes. These zinc complexes serve as promising emissive layers for optoelectronic applications [107].

6.3 Sensing applications

Fluorescence on/off sensor of a wide range of Schiff bases is being developed for determination of various analytes, toxic ions, and metallic cations and anions in different types of environmental and biological media [108].

Biosensor: Conductive hydrogels based on graphene oxide, dopamine, and polyacrylamide were prepared using the Schiff bases. The high elongation, toughness, and self-adhesion of conducting hydrogels have provided great advantages as biosensors [109].

In forensics, Schiff bases are primarily used in the analysis of illicit drugs. Chemical reactions with Schiff bases reveal illicit drug production and help determine analytes in confiscated samples [110, 111].

6.4 Tissue regeneration

Various substituted Schiff bases have enhanced bulk modulus of the composite hydrogels and slightly increased the in vitro degradation rate. It also promoted cell adhesion and proliferation and maintains the regular cell morphology of bovine articular chondrocytes, increasing potential applications in cartilage tissue engineering [109].

6.5 Bioprint

Water-soluble hydroxybutyl chitosan (HBC) and chondroitin oxysulfate (OCS) have been used to generate bioinks based on the Schiff base reaction, using different sacrificial molds in 3D bioprinting techniques to produce different structures of hydrogels. The controllable shape of HBC/OCS bionic hydrogels can be optimized and customized for specific cartilage engineering applications [109].

6.6 Tissue adhesion

Aldehyde groups in hydrogels based on the Schiff reagent can promote the adhesion of hydrogels to surrounding tissues. An injectable double-cross-linked self-healing hydrogel based on dopamine-grafted oxidized sodium alginate (OSA-DA) and polyacrylamide (PAM) for wound healing has been reported. In terms of hydrogen bonding and Schiff base bonding, the self-healing OSA-DA-PAM hydrogel possesses stable mechanical properties such as high tensile strength and elongation. In addition, numerous catechol groups on OSA-DA chains can endow hydrogels with unique cell affinity and tissue adhesion [10]. In situ forming hydrogel, derived from natural polysaccharides through Schiff base reaction, can be modulated and prepared for soft tissue adhesive, hemostasis, or other biomedical applications in future [110].

6.7 Dyes

New complexes of Zn(II), Pd(II), and Pt(II) with Schiff bases are metal salts of 4-(dibutylamino)-2-hydroxybenzaldehyde and 4,5-diaminophthalonitrile. Sensor applications for imaging surface temperature (planar optodes) and monitoring rapid temperature changes (fiber optic microsensors) have been demonstrated. Pt(II) complexes immobilized in gas permeable matrices also turned out to be promising materials for oxygen measurements. [112].

Schiff bases based on salicylaldehyde units and their use as metal-free organic chromophores can be used to sensitized and co-sensitize dye-sensitized solar cells (DSSCs) [113].

Compounds Et2N-L-SnPh2 and MeO-L-SnPh2 act as an excellent staining for cancer cells (HeLa) using two-photon bioimaging and are expected to have biomedical applications [104].

7. Future prospectus

From the discussion in the section of biological evaluation of Schiff bases, it was clear that the pharmacophore possesses various biological activities, which can be again explored more against various diseases. New groups of organic compounds are still being described, the combinations of which may form a group of extremely desirable compounds with higher potential. The biologically active Schiff's base ligands and metal complexes are playing very crucial role in the drug discovery [114]. Medicinal chemists are now interested in developing novel chemotherapeutic Schiff bases and their metal complexes.

Apart from this, conjugated Schiff Bases have been employed in electronics such the organic field-effect transistor, Perovskite solar cells, and electrochromic devices because they offer some intriguing optoelectronic features. These are also employed in the production of covalent organic framework, which is used in the storage of gas [115]. The measurement of pH values has evolved into one of the most essential necessities with the recent advancements in biological and environmental research. Because of their smooth synthetic roots, easily tuneable structural architecture, non-destructive signals of emission, visually differentiable color generation, and capacity for real sample analysis, organic Schiff base compounds and their derivatives have been observed to play crucial roles in determining the pH values of a particular medium [116]. Because of its bioactive core, Schiff bases have a wide range of applications in the chemical, food, coordination, medical, agricultural, and other industries. This body of literature made it very evident that there will be several opportunities for Schiff bases to become active research molecules in the future.

8. Conclusion

Schiff bases are integral core of the organic chemistry having a verity of biological activities. This chapter focused on the novel leads of numerous Schiff bases having potential medicinal activities with lesser side effects. At last decades, the researchers perceived attention toward bioactive core of Schiff bases, which gained wide medicinal interest. This chapter also explored industrial application of Schiff bases. Advances in this era will require access of the structure activity relationship and mechanism of action of the Schiff bases containing compounds.

At present scenario, Schiff bases are perceived importance in biological activity. It is a versatile organic compound, which is synthesized in reaction between amino compound and aldehyde or ketone well known as imine by condensation process. This imine or azomethine functional groups are versatile pharmacophores for design and development of various bioactive lead compounds. Schiff bases are extensively used for biological activities such antimicrobial, anthelmintic, anti-inflammatory, anticonvulsant, antiTB, antineoplastic, and antidepressant activities. Also, Schiff bases have an intermediately compound in synthesis of various organic compounds. It is also used as catalyst, pigments, and dye synthesis. Furthermore, Schiff bases are used as corrosion inhibitors. The metal complexes of Schiff bases have diversified biological activities. The present chapter summarized the information with respect to diverse biological activities and depicted the recent synthesized variety Schiff bases as potential bioactive core.

Conflict of interest

We confirm that there is no conflict of interest.

Author details

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