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Review Article **Open Access**

Review: Synthesis and Applications of Schiff Bases

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A B S T R A C T

Schiff bases are obtained by condensation of aldehyde with primary amine. It is also called as imine. Since first synthesis of imine, number of methods has been discovered to enhance reaction yield, decrease reaction time as well as reduce hazardous reagents and reaction conditions. Compound with Schiff base core are widely used for industrial purposes and also exhibit a broad range of biological activities. An overview of synthetic methodologies used for the construction of Schiff base is also described.

Keywords: Schiff base, synthetic methodology, biological applications.

A R T I C L E I N F O

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1. Introduction

Schiff bases, named after Hugo Schiff [1], who has been discovered reaction of any primary amine with an aldehyde or a ketone. Schiff base (imine or azomethine) is analogous to aldehyde or ketone in which the carbonyl group (C=O) is

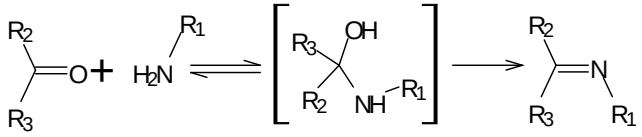
replaced by an azomethine or imine group. The Schiff bases are most widely used nitrogenous organic compounds. They are used as dyes and pigments, catalysts, intermediates in organic synthesis, as well as polymer stabilizers [2]. Schiff bases exhibit a broad range of biological activities like antibacterial, antifungal, antimalarial, antituberculosis, antiviral, anti-inflammatory, and antipyretic properties [3]. Imine or azomethine groups are present in various natural and synthetic compounds. The imine group from Schiff base has been shown to be critical to their biological activities [4].

Imine was first prepared in the 19th century by Hugo Schiff (1864). Since then a variety of new methods for the synthesis of imines have been developed [5]. The well-known synthesis was reported by Schiff involves the condensation of a carbonyl compound (aldehyde or Ketone) with an amine under azeotropic distillation [6]. Molecular sieves were then used for removal of water formed in the reaction mixture to enhance the rate and yield of reaction [7]. In the 1990s in-situ method for dehydration was developed, using dehydrating agents like tetramethyl orthosilicate or trimethyl orthoformate [8-9]. In 2004, Chakraborti et al. [10] explained that the efficiency of these processes is dependent on the use of highly electrophilic carbonyl compounds and strongly nucleophilic amines. Alternatively Bronsted-Lowry or Lewis acids can be used to activate the carbonyl group of aldehydes or ketones, catalyze the nucleophilic attack by amines, and remove the water from the system. Examples of Bronsted-Lowry or lewis acids or dehydrating agents used for the synthesis of Schiff bases include $ZnCl_2$, $TiCl_4$, $MgSO_4$-PPTS, $Ti(OR)_4$, alumina, H_2SO_4, $NaHCO_3$, $MgSO_4$, NaCl, $Mg(ClO_4)_2$, H_3CCOOH, $Er(OTf)_3$, P_2O_5/Al_2O_3, HCl, CH_3COOH, etc [11–12]. In the past few years a number of new techniques for synthesis of Schiff base have been developed such as microwave irradiation, solvent-free, clay, solid-state synthesis, ionic liquid [bmim]BF_4, molecular sieves, infrared irradiation, $NaHSO_4$, SiO_2, and ultrasound irradiation [13–15]. Among these innovations, microwave irradiation is most effective because of its simple operation, enhanced reaction rates and great selectivity. Rousell and Majetich groups independently studied the use of microwave irradiation [16-17]. Microwave irradiation is less hazardous to environment than other methods because it reduces the excessive use of organic solvents. Another important merit of this technique is that the reactions achieve high efficiency in a shorter period of reaction time.

2. Methods of preparation of Schiff Bases

2.1 Reaction of Aldehydes and Ketones with Amines

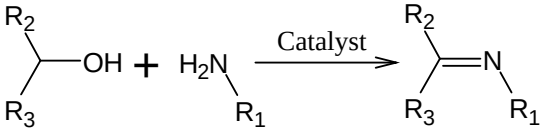
The reaction of an aldehyde or ketone reacts with a primary amine with elimination of one water molecule gives imine as a product. The rate of reaction is accelerated by acid catalysis and also it is commonly carried out by refluxing a mixture of a carbonyl compound and an amine, in a Dean Stark apparatus to remove the water from reaction mixture. This dehydration is important to convert aminal into the imine as it is reversible. From these observations several dehydrating agents have been successfully used. [18-19]. Acid catalyst is required for activation of carbonyl carbon, mineral acids like HCl or H_2SO_4, organic acids such as pyridinium *p*-toluenesulphonate or *p*-toluene sulphonic acids, acetic acid, acid resins as well as Lewis acids like $ZnCl_2$, $TiCl_4$, $SnCl_4$, BF_3Et_2O, $MgSO_4$, $Mg(ClO_4)_2$, *etc*., have been reported. [20-21]



Imines formation reaction of aliphatic ketones is slower than aldehydes; therefore it requires higher reaction temperatures and longer reaction time. Acid catalysts and dehydrating agent can significantly increase the reaction yields, which can reach 80%–95% values. Aromatic ketones are less reactive than aliphatic ketones and require harsh conditions to be converted into imines [22]. Recently many new techniques to synthesize imines have been reported in various research journals for such less active carbonyl compounds. [23–24].

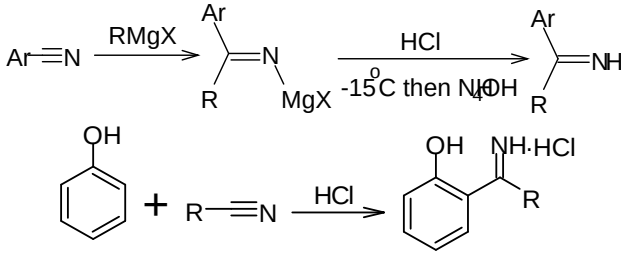
2.2 Aerobic Oxidative Synthesis

Aldehydes and ketones can be obtained by oxidation of the corresponding alcohols. Straightforward preparations of imines from amines and alcohols have recently been developed [25–27].



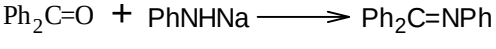
2.3 Addition of Organo-metallic Reagents to Cyanides

Alkyl and aryl cyanides react smoothly with Grignard reagent to produce ketimines with good yields in the presence of an acid catalyst [28–29]. The mixture of nitrile and phenol is prepared in ether and solution is saturated with HCl gas, but for less reactive phenols $ZnCl_2$ is required to be added.

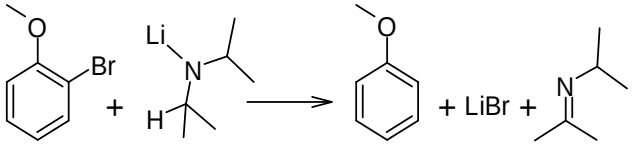


2.4 Reaction of Metal Amides.

Addition reactions of alkali metal amine salts to aromatic ketones produce ketimine. The scope of this reaction has been widely extended.

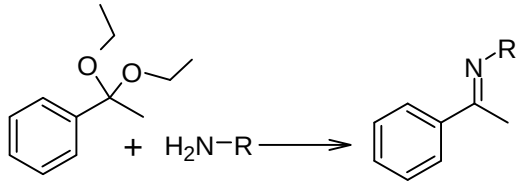


Oxidation of metalloamines having α-hydrogen by 2-bromoanisole leads to formation of imine [30].



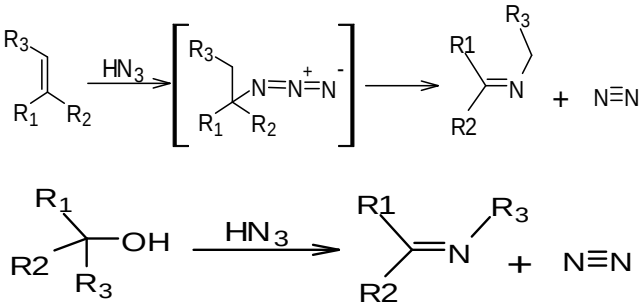
2.5 Synthesis of ketimines from ketals

The ketimines can be prepared with good yield using aryl ketone diethyl ketals and arylamines, but for alkylamines yield is very low [31]. Similarly, imines can react with higher boiling point amines to give the exchange products. This further distilled to drive equilibrium towards the formation of the desired product [32].



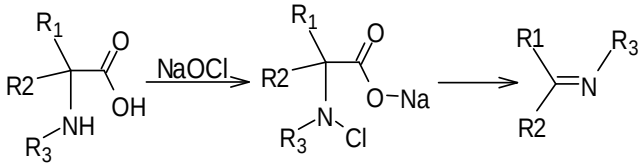
2.6 Reaction of olefins and tertiary alcohols with hydrazoic acid.

The ketimines can be synthesized by treating olefins and tertiary alcohols with hydrazoic acid in H_2SO_4. [33]



2.6 Reaction of amino acids with sodium hypochlorite.

Imines can also be formed by reaction of amino acids on treatment with sodium hypochlorite. In the first step of this reaction chloramine is formed as an intermediate subsequently converted to imine by elimination of carbon dioxide and sodium chloride [34].

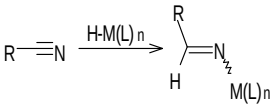


2.7 Preparation of N-Metallo-Imines

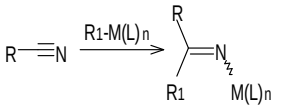
The *N*-metallo-imines constitute a new family of organometallic compounds congeners of Schiff bases [35]. They have been found synthetic applications as stable analogues of the corresponding Schiff bases. This research work has been fully explored by the Barluenga [36–38], Ghosez [39-40] and Panunzio groups [41–43]. They are monomeric compounds stable only under anhydrous conditions. Since the metal-nitrogen bond is easily undergo hydrolysis, the *N*-metalloimines can be considered as protected and stabilized form of the corresponding elusive imines of ammonia, which are very unstable readily undergo trimerize to triazines. Although some stable metalloimines like silylimines of certain aldehydes can be isolated in a pure form by distillation under reduced pressure. But in practical it is more convenient to prepare them *in situ* just before the use.

2.7.1 Preparation of *N*-metalloimines from nitriles

Nitriles undergo addition reaction with organometallic reagents or a metallo hydride to yield N-metalloimines. [44–45]



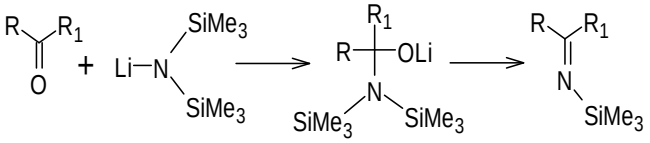
R=Alkyl, Aryl. M=Al, B.



R=Alkyl, Aryl. R_1=Alkyl, Aryl. M=Li, Mg.

2.7.2 Preparation of *N*-Silylimines

Among the different metalloimines, *N*-trialkylsilyl imines must be considered the most popular and the most used intermediates in the synthesis of nitrogen containing organic compounds, with special emphasis to the potentially bioactive ones. For the first time Silyl imines have been synthesized by Rochow [46] involve reaction of aromatic aldehydes and nonenolizable ketones with one equivalent of lithium hexamethyldisilylamide in tetrahydrofuran [47]. The reaction proceeds by an addition-elimination sequence probably involving a four centers cyclic transition state.

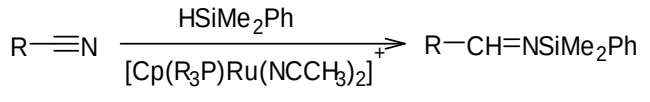


R=Alkyl or Aryl; R_1=H, Alkyl or Aryl

Silylimines cannot be synthesized from ketones bearing α-hydrogen atom because the strongly basic organometallic reagent attacks α-hydrogen affording the corresponding lithium enolate. The aldehydes which are enolizable were supposed to behave in the same way [48].

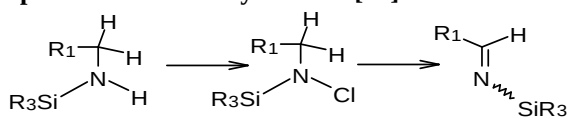
2.8.3 N-alkylsilyl imines via hydrosilylation of nitrile.

Recently Nikonov and co-workers [49] reported an elegant preparation of N-silylaldimines via a chemoselective hydrosilylation of nitriles catalyzed by ruthenium complex.



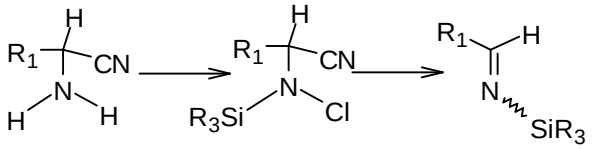
4-5 mol %

2.8.4 Formation of silylimines via elimination of vicinal groups from *N*-chlorosilylamines. [50]



R_1=Ph, 2-Furyl, COOEt, -CH=CH₂

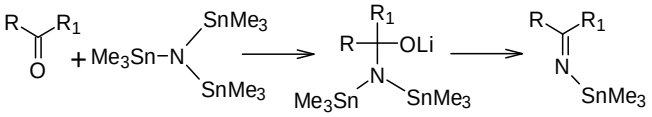
2.8.5 Formation of silylimines via elimination of vicinal groups from α-cyanosilylamines. [51]



R_1= H, Me, Et, n-Pr

2.9 Preparation of *N*-tin-imines via reaction of carbonyl compounds with tris(trimethylstannyl)amine

This method allows the preparation of tin imines from aldehydes and ketones. Adavantages of this method are good reaction yield and very mild reaction conditions. Rochow's procedure involves an addition-elimination reaction. The organometallic reagent, tris (trimethyl stanny1) amines which can be easily prepared from trimethyl tin chloride and lithium amide. Tris(trimethylstanny1)amine show weak basic properties therefore the α-deprotonation is completely suppressed. This is allowing a facile preparation of tin-imines even in the case of enolizable ketones and aldehydes. An interesting feature of the tin-imines is the possibility to undergo transmetallation reactions with trialkylsilyl chlorides (e.g., chloro tert-butyl dimethyl silane) to give the corresponding N-silylimine and tris(trimethyltin)onium chloride that spontaneously precipitates from the solution. It is then filtered to get pure solution of silylimines. [52]



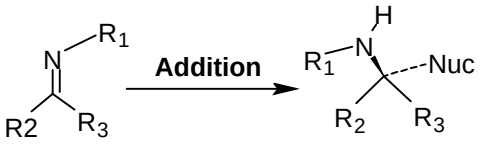
R=Alkyl or Aryl; R_1=H, Alkyl or Aryl

3. Importance of Schiff Bases

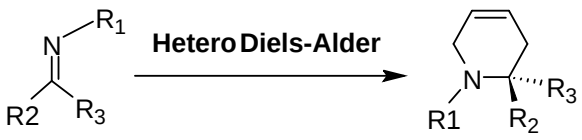
3.1 Applications of Schiff bases in organic synthesis

Schiff bases are versatile precursor for organic syntheses. Four different types of reactions in which Schiff bases have been found extremely important applications:

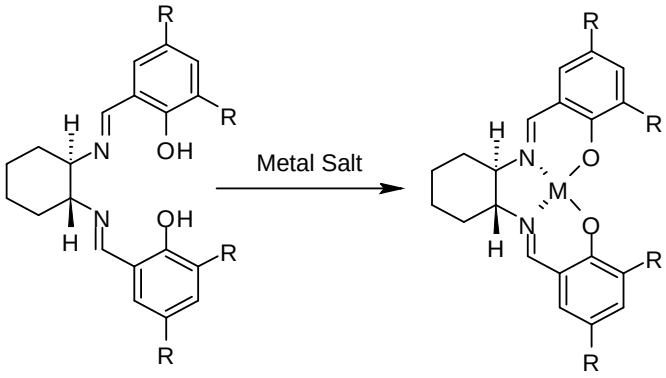
(a) Reduction of C=N bond, focused on asymmetric formation of carbon-carbon bond [53]



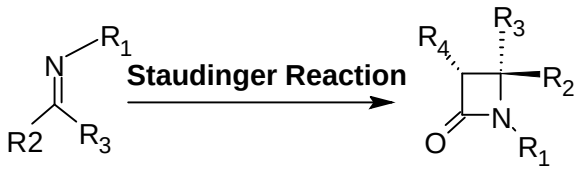
(b) Hetero Diels-Alder reactions with the formation of heterocyclic compounds [54]



(c) Use of chiral salen metal complexes in the asymmetric synthesis [55–56] salophen metal complex as catalysts [57–60].

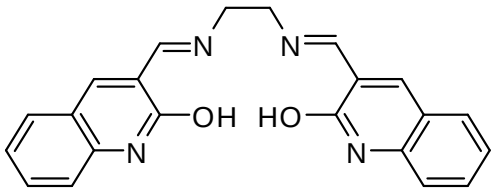


(d) Staudinger reactions for the preparation of β-lactams [61–62].

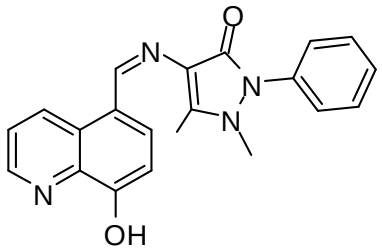


3.2 Fluorescence Devices

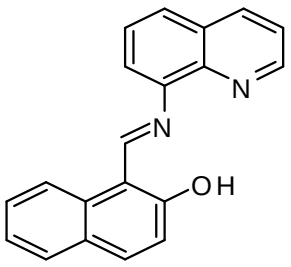
a) A novel fluorescent chemosensor for Zn (II) based on 3,3'-{ethane-1,2 diylbis [nitrilo(*E*) methyl ylidene]} diquinolin-2-ol introduced by Zeng-chen Liu et al. in 2010. [63]



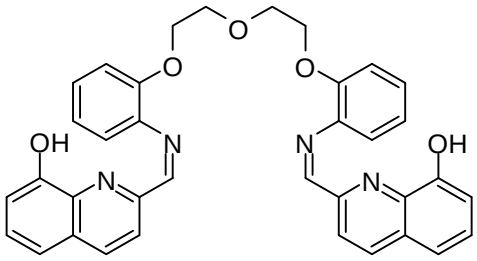
b) Xin-hui Jiang et al. (2011) worked on 8-Hydroxyquinoline-5-carbaldehyde Schiff-base as a highly selective and sensitive Al^{3+} sensor in weak acid aqueous medium. [64]



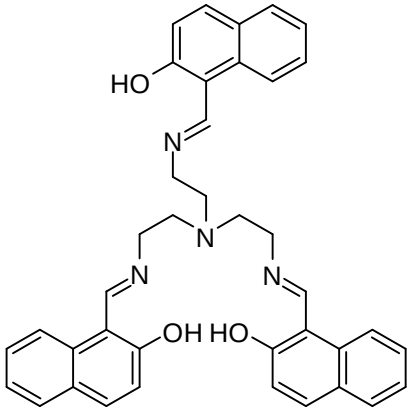
c) Hyun Min Park et al. developed a turn-on fluorescence method to detect Al^{3+} using a quinoline–naphthol-based chemosensory with high selectivity. [65]



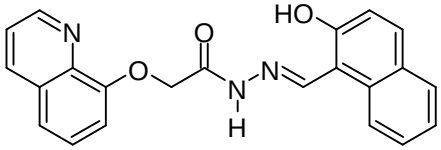
d) Javier Fernández-Lodeiro et al. have been done synthesis of fluorescence materials based on 8-OH-quinoline. [66]



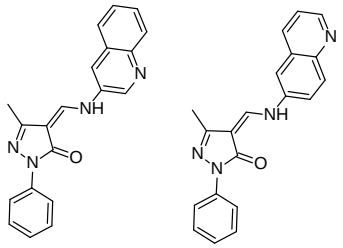
e) Research group Wei Hsun Hsieh et al in 2012 developed a turn-on Schiff base fluorescence sensor for Zinc ion. [67]



f) β-Hydroxy-α-naphthaldehyde [2-(quinolin-80-yloxy) acetyl] hydrazone was reported as an efficient fluorescent chemosensor for Mg^{2+} by Jing-can Qin et al. in 2015. [68]

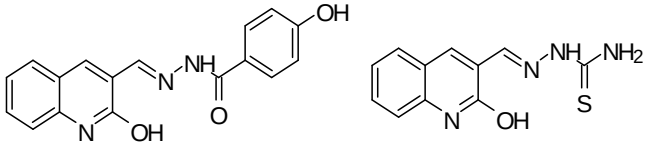


g) Photo- and electroluminescent properties of zinc (II) complexes with aminomethylene derivatives of 1-phenyl-3-methyl-4-formylpyrazol-5-one and 3- and 6-aminoquinolines was studied by Anatolii S. et al. [69**]**

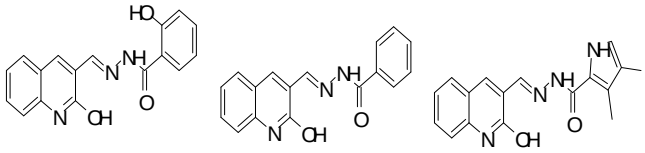


3.3 Biological Applications: DNA interaction, antioxidant, cytotoxicity

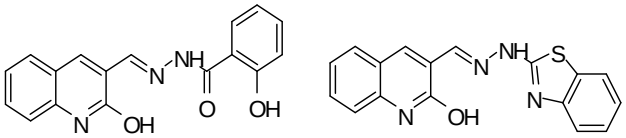
a) Synthesis, crystal structure, DNA interaction and antioxidant activities of two novel water-soluble Cu (II) complexes derived from 2-hydroxyquinoline-3-carbaldehyde Schiff-bases reported in European Journal of Medicinal Chemistry. [70]



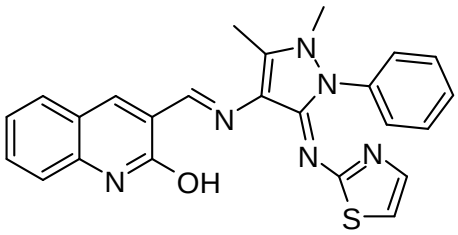
b) Zeng-Chen Liu et al reported Crystal structures, DNA-binding and cytotoxic activities studies of Cu(II) complexes with 2-hydroxyquinoline-3-carbaldehyde Schiff-bases in 2010. [71]



c) Gurunath S. Kurdekar et al. in 2011 explained the synthesis, characterization, antibiogram and DNA binding of novel Co(II), Ni(II), Cu(II), and Zn(II) complexes of Schiff base ligands with quinoline core. [72]

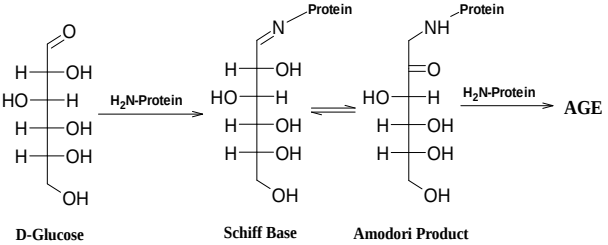


d) Senthil Kumaran et al. reported biologically important Cu(II), Co(II), Ni(II) and Zn(II) complexes of tetradentate Schiff base ligand. [73]



3.4 Schiff Bases as intermediate of bio-processes

The glycation of albumin that leads to the formation of important biomarkers, which are predictive of type II diabetes [74] or to the reaction between sugars and biologically relevant amines with the formation of Schiff bases. These intermediate Schiff bases in turn modified to advanced Glycation endproducts (*AGE*) through Amadori compounds. *AGEs* are involved in many pathological conditions such as cardiovascular disease, Alzheimer [75] and so on.



Protein glycation by glucose

3.3 Application of Schiff Bases in Pharmaceutical Research.

There are numerous publications covering the use of Schiff bases in therapeutic or biological applications either as potential drug candidates or diagnostic probes and analytical tools. The activity of Schiff bases as anticancer compounds [76-77] including radioactive nuclide complexes, antibacterial [78–80], antifungal [81-83], antiviral agents [84], has been extensively studied. Moreover, Schiff bases are present in the form of various natural as well as synthetic compounds and have been demonstrated to be essential for their biological activities [85].

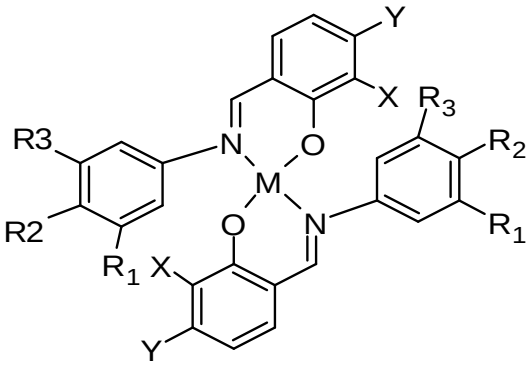
3.4 Anti- parasitic Schiff Bases.

Malaria is a severe morbidity of humans and other animals. It is caused by protozoa of the genus Plasmodium. A bite from an infected female Anopheles mosquito introduces the Plasmodium parasite into the blood circulatory system through contaminated saliva.Through blood circulation these parasites travel to the liver to mature and reproduce. Common symptoms of malaria include periodic fever, shivering, anaemia and enlargement of spleen, which in severe cases can progress to coma and eventually death.

The imino-group (C=N) of Schiff bases necessary to show antimalarial activity. For example, ancistrocladidine a secondary metabolite produced by plants belonging to the families Ancistrocladaceae and Dioncophyllaceae having an imine group in its structure. The compound has shown potent activity against P. falciparum K1. Some novel Schiff bases synthesized by reacting 1-formyl-5-nitroisoquinoline with amines showed activity against a chloroquine-resistant Plasmodium falciparum strain (ACC Niger) [86**]**.

3.5 Salicylidene Amines as bioactive compounds

Salicylidenebenzylamine derivatives have been studied extensively for their biological activities [87–88]. Schiff base complexes derived from 4-hydroxysalicylaldehyde show strong anticancer activity e.g., against Ehrlich ascites carcinoma (EAC) [89**]**. On other hand *N*-(salicylidene)-2-hydroxyaniline showed activity against *Mycobacterium tuberculosis* H37Rv. The antibacterial activity of a series of 5-chlorosalicylaldehyde-Shiff bases was studied against several strains including *Escherichia coli* and *Staphylococcus aureus*. Cu (II) and Cd (II) complexes of more highly functionalized salicylidenebenzylamines present higher activity with respect to the free molecules [90].

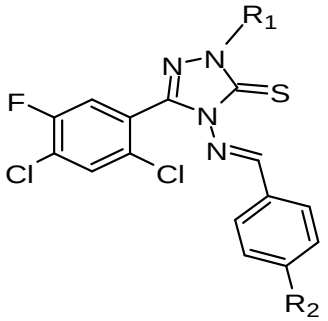


Cu (II) and Cd (II) complexes of salicylidenebenzylamines

Compound	X	Y	R_1	R_2	R_3
a	OH	OH	H	Br	H
b	OH	OH	tBu	OH	tBu
c	OH	H	H	Me	H
d	OH	H	H	Br	H
e	H	OH	tBu	OH	tBu

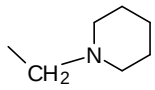
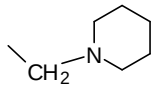
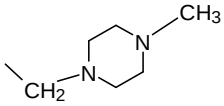
3.6 Other Antibacterial Schiff Bases

Schiff bases characterized by a 2,4-dichloro-5-fluorophenyl moiety completely inhibited the growth of different microorganisms such as S. aureus, E. coli, Pseudomonas aeruginosa, and Klebsiella pneumoniae with comparable MIC values with ciprofloxacin ranging from 6.3 to 12.5 µg/mL [91**]**.



Chemical structure of 2,4-dichloro-5-fluorophenyl Schiff bases.

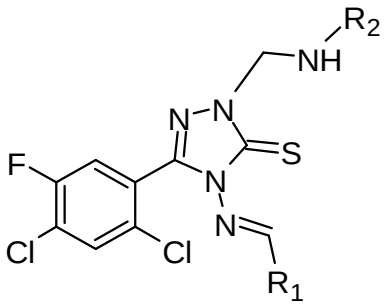
Table 2

Compound	R_1	R_2
a	-H	$-OCH_3$
b		$-NMe_2$
c		-Cl
d		-Cl

The secondary metabolites of the plant Actinomadura rubra, madurahydroxylactones, have been transformed into the corresponding Schiff bases [92]. Madurahydroxylactone-derived compounds shows good inhibition against B. subtilis, Micrococcus flavus, Sarcina lutea, and S. aureus giving MIC values varying from 0.2 to 3.1 µg/mL [93].

3.7 Antifungal Schiff Bases

The imine derivatives having a 2,4-dichloro-5-fluorophenyl moiety and the Schiff bases inhibited the growth of different fungi such as Trichophyton mentagrophytes, Aspergillus fumigatus, Penicillium marneffei, Aspergillus flavus. The compounds showed MIC values in the range of 6.3–12.5 µg/mL, which is comparable to that of fluconazole. The isatin-derived Schiff bases showed an interesting activity against Microsporum audouinii (MIC 2.4–9.7 µg/mL) and Microsporum gypseum (MIC 1.2–9.7 µg/mL) [94].



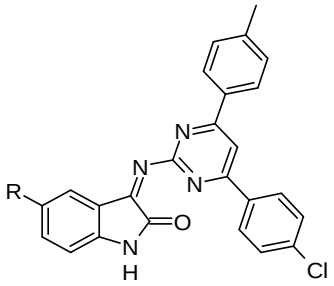
Antifungal Schiff bases derived from 2,4-dichloro-5-fluorophenyl scaffold

Compound	R_1	R_2
A	4-F-C_6H_4	4-Cl-C_6H_4
B	3-Cl,4-F-C_6H_3	4-Cl-C_6H_4
C	4-F-C_6H_4	piperonyl
D	3-Cl,4-F-C_6H_3	piperonyl

The compounds reported inhibited also *Candida albicans*, *Aspergillus niger*, *Cryptococcus neoformans*, *T. mentagrophytes*, *E. floccosum*, and *Histoplasma capsulatum* (MIC range 10–79 µg/mL) [95].

3.8 Antiviral Schiff Bases

The Schiff bases of modified 3-hydroxyguanidines [96**],** have been prepared and tested against mouse hepatitis virus (MHV), in particular, compound inhibited the viral replication by 50% when used at a concentration of 3.2 µM.



Isatin derived Schiff bases. R=H, Br, Cl

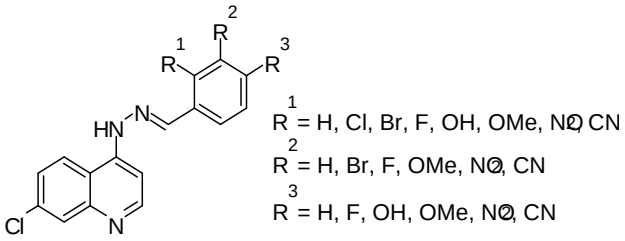
Similarly, a set of imine derivatives of abacavir [97] have been prepared and tested for their antiviral activity. Compounds were highly potent against the human immunodeficiency virus-type 1 (HIV-1).

3.9 Hybrid Structures.

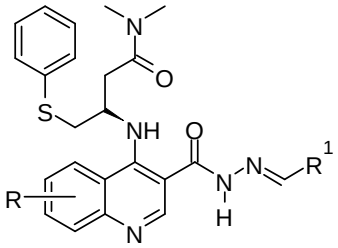
The use of hybrid structures to achieve new pharmacological activities is widely used in medicinal chemistry. In an attempt to achieve novel antitumor compounds, Schiff and Mannich bases of fluoroquinolones have been prepared and tested in cell line. Particularly hybrid fluoroquinolone-Schiff bases compounds showed good activity against, HL60, CHO and L1210 tumor cells in the MTT assay [98].

3.10 Anti-tuberculosis Schiff Bases and Hydrazones

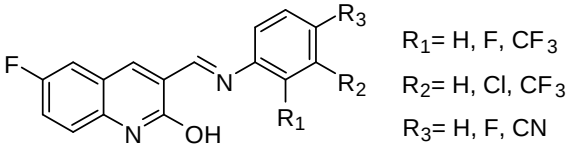
a) A series of twenty-one 7-chloro-4-quinolinylhydrazones have been synthesized and evaluated for their in vitro antibacterial activity against Mycobacterium tuberculosis H37Rv. These compounds exhibited MIC between 12.5 and 2.5µg/mL [99].



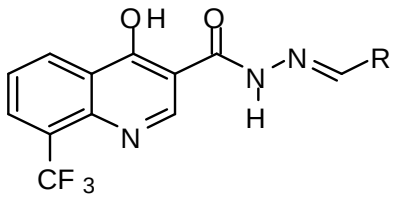
b) The new quinoline derivatives carrying active pharmacophores has been synthesized and evaluated for their in vitro antituberculosis activity against Mycobacterium tuberculosis H37Rv (MTB), Mycobacterium smegmatis (MC2), and Mycobacterium fortuitum following the broth micro dilution assay method [100].



c) The series of Schiff bases containing quinoline core and their Zn (II) and Cu (II) complexes have been synthesized and evaluated for their anti-TB activity. These compounds have shown MIC values in the range of 1.6-3.2 µg/mL against Mycobacterium tuberculosis H37Rv [101].



d) The Schiff base hydrazones containing quinoline core were evaluated for their antimicrobial activities including antimycobacterial activity. Most of the compounds exhibited excellent biological activities [102].



4. Conclusion

Schiff base compounds have been widely explored for industrial applications. However, the biological activity of this class of compounds deserves further investigation. Although the research on this subject is incipient, a number of reports disclosing the effects of the Schiff base compounds on the pathogens of clinical interest have recently been increasing. Compounds containing Schiff base core have been shown to be promising leads for the design of more efficient antimicrobial agents. Advances in

this field will require analyses of the structure activity relationships of the Schiff base compounds as well as the mechanism of action of these compounds.

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