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Schiff Bases: Versatile Motifs of Synthetic and Biological Interest

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***Abstract**:*
Schiff bases are versatile compounds with a series of applications, from synthetic to biological to technological spheres. There was a lots of development took place in recent years in the field of Schiff bases due to their broad spectrum of applications. The presence of reactive C=N function in Schiff bases makes them as more versatile scaffolds for the synthesis of varied classes of biologically active heterocycles, complex compounds with transition metal ions. The Schiff base derivatives themselves possesses wide range of biological activities, and also known to have physical properties like non-linear optical, fluorescence properties. In this pretext, this review discusses overall developments in the synthetic procedures, utility as scaffolds in synthesis, biological applications in particular, their antimicrobial, antidiabetic, antiproliferative, anticancer, anti-Alzheimer and physical properties of Schiff bases. The critical discussion was made on recent advances in the synthetic and biological applications might be useful for the researchers working in this area.

***Keywords**: Antimicrobial, anticancer, antidiabetic, anti-inflammatory, complex, synthesis.*

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I. Introduction

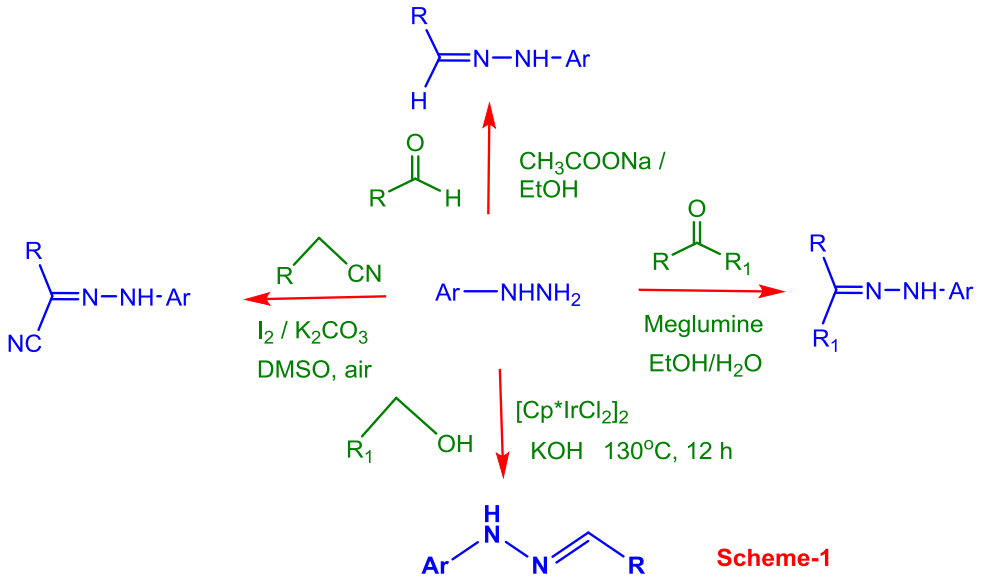
Schiff bases are the class of compounds that contains C=N- functionality. Generally, these class of compounds were obtained by the condensation reaction of carbonyl compounds viz. aldehydes or ketones with amines, hydrazines, and acid hydrazides under appropriate reaction conditions. The presence of reactive –C=N- function in Schiff bases makes them a versatile scaffold in organic synthesis. Literature reveals that, Schiff bases are generally prepared by the acid or base catalyzed condensation reaction of aldehydes or ketones with amines, hydrazines, and hydrazides under appropriate reaction conditions [1]. These class of compounds have been extensively used as building blocks in the synthesis of almost all classes of heterocycles of biological interest through various methods like, click reaction, 1,3-dipolar cycloaddition, (3+2) annulation, Diels-Alder reaction, etc, [2]. The unshared pair of electrons of the nitrogen of C=N- function makes these as susceptible molecules to undergo complexation with various metal ions to form coordination compounds of biological activity and physicochemical properties [3].

Schiff base derivatives themselves were known to have enormous amount of diversified biological activities like antimicrobial, antioxidant, anti-cancer, anti-inflammatory, antidiabetic, anti-ulcer etc. There has been a considerable development in the synthetic strategies aiming towards accessibility, easy procedure, good yields, stereoselectivity, eco-friendly reaction conditions, and also their utility in synthetic and pharmacological applications in recent years. The recent review on 1,3,4-thiadiazole containing Schiff base moiety highlight their pharmacological activities [4]. In this view, the present review explores the synthetic strategies, utilities in synthetic and medicinal applications developed in in the field of Schiff base derivatives in last decade or so.

II. Synthesis and Synthetic Applications

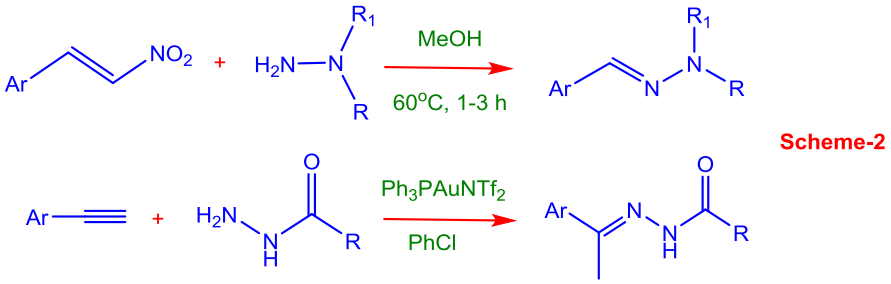
The simplicity of the preparation allows for a great chemical variability and synthetic manageability of Schiff bases. However, the process can be not as straightforward as one would imagine, the parameters such as specific reactants, the amount of acid/base employed as catalyst, reaction time and temperature etc., can have a direct impact on the product. Although, numerous methods have been developed for the synthesis, but most commonly employed method being acid or base catalyzed condensation of carbonyl compounds with amines, hydrazines, acid hydrazides, this is because of its simplest procedure to perform to get desired Schiff base analogues (**Scheme-1**). For instance, a simple, environmentally benign protocol was developed for synthesis from carbonyl compounds and hydrazides in the presence of meglumine in aqueous ethanol at room temperature (**Scheme-1**) [5]. The salient features of the protocol being mild reaction conditions, short reaction time, high yields, operational simplicity, metal-free, applicability toward large-scale synthesis, and biodegradable and inexpensive catalyst. The iodine mediated diazenylation of active methylene compounds with arylhydrazine hydrochlorides in basic aerobic conditions executed either under heating or in the presence of blue LED light

(**Scheme-1**) [6]. A catalytic acceptorless dehydrogenative coupling of arylhydrazines and alcohols enables a direct synthesis of arylhydrazones with complete selectivity for arylhydrazones without *N*-alkylated byproducts (**Scheme-1**) [7]. The method provides new horizon for the development of catalytic acceptorless dehydrogenative coupling.



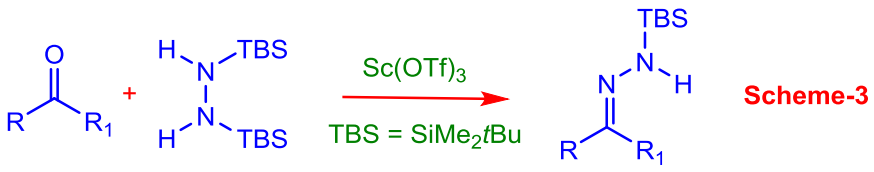
Scheme-1

The Michael addition of amines and hydrazines to nitrostyrenes provides *N*-substituted benzyl imines and *N*-substituted benzyl hydrazones via a retro-aza-Henry-type process under mild, and non-catalytic conditions. The method can be used for the synthesis of biologically important *N*-methyl pyrazoles in a one-pot manner, from simple starting materials nitrostyrenes and the methylhydrazine (**Scheme-2**) [8]. A group of researchers reported the synthesized two Schiff bases viz. (*E*)-2-(1-(2-phenylhydrazono)ethyl)naphtholen-1-ol and (*E*)-2-(1-(2-(4-chlorophenyl)hydrozono)ethyl)naphtolen-1-ol by the reaction of 1-(1-hydroxynaphthalen-2-yl)ethan-1-one with phenylhydrazine and 4-chlorophenylhydrazine, respectively in the presence of sodium acetate in ethyl alcohol under reflux conditions [9, 10]. The study showed that the products formed with trans configuration around C=N bonds. A gold-catalyzed hydrohydrazidation of alkynes with hydrazides to form substituted keto-*N*-acylhydrazones under mild conditions was developed (**Scheme-2**) [11]. The method exhibits high functional group tolerance, and is insensitive to electronic and steric effects.



Scheme-2

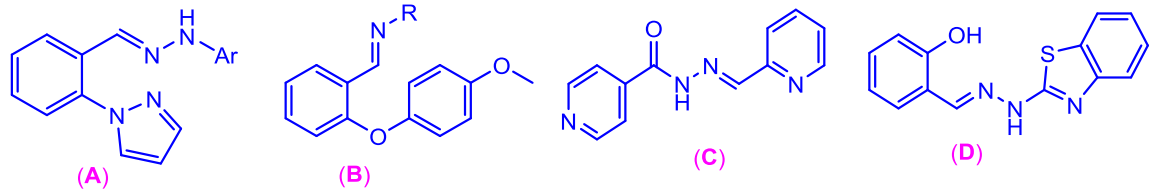
The condensation of aromatic aldehydes with phenylhydrazine in the presence of sodium acetate produced hydrazine Schiff bases in excellent yields [12]. *N*-tert-butyldimethylsilylhydrazone derivatives serve as superior alternatives to simple hydrazones in Wolff-Kishner-type reduction reactions, Barton vinyl iodide preparation, and synthesis of *gem*-dihalides. To check their vulnerability, *N*-tert-butyldimethylsilylhydrazone derivatives were synthesized by the reaction of ketones and 1,2-bis(tert-butyldimethylsilyl)hydrazine in the presence of metal triflate $Sc(OTf)_3$ **(Scheme-3)** [13]. In an attempt to synthesize formyl(pyrazole), The reaction of 2-acetylthiophene, phenylhydrazine and an alkene in the presence of $POCl_3$ in DMF, yielded an unusual product (*E*)-*N*-phenyl-*N'*-[1-(thiophene-2-yl)ethylidene]formohydrazide [14], was characterized by crystallographic studies.



Scheme-3

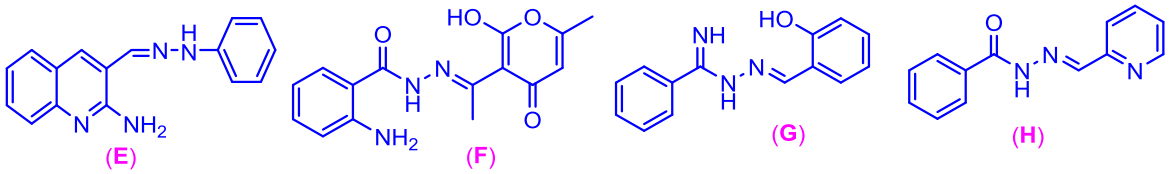
The hydrazine Schiff bases have been extensively used as a precursor in 1,3-dipolar cycloaddition reactions *en route* to the synthesis of pyrazole derivatives [15]. The reaction proceeds through catalytic dehydrogenation of hydrazones with mild oxidizing agents like, NBS, chloramine-T, sodium hypochlorite, mercuric acetate, manganese dioxide etc., to form an intermediate nitrile imines as 1,3-dipolar ion [16], which undergo cycloaddition with dipolarophile to form pyrazoles [17]. Two sets of isoniazid-derived compounds (*E*)-1-(2-((2-phenylhydrazineylidene)methyl)phenyl)-1*H*-pyrazole (**A**) and (*E*)-1-(2-(4-methoxyphenoxy)phenyl)-*N*-phenylmethanimine (**B**) prepared from a pair of different aldehydes under drastic conditions lead to unexpected dihydrazones. 2-(1*H*-pyrazol-1-yl)benzaldehyde a precursor of compound (**A**) was unexpectedly obtained *via* the copper-catalyzed Ullmann C–N coupling between 2-bromobenzaldehyde and pyrazole. The theoretically-based reaction pathway for the unexpected formation of the dihydrazones, involve the solvolysis of the formed isonicotinoyl hydrazone followed by attack to a second free aldehyde molecule [18]. The reduction of Schiff bases by using sodium borohydride as a selective reducing agent forms secondary amines [19]. The Schiff base motifs were efficiently transformed to dye stuffs of diverse applications [20, 21].

The Schiff base (2-pyridinecarbaldehyde isonicotinoyl hydrazone) (**C**) was able to form complex with cd(II) metal ions, the resulting metal complexes could bind with the calf thymus-DNA via intercalation with the binding strength in the order of complexes > ligands [22]. The hydrazone Schiff base derivatives were efficiently transformed in to formylpyrazoles [23], bis(formylpyrazoles) [24, 25], formohydrazides [26] via Vilsmeier Hack reaction. The unshared paired of electrons on the nitrogen atom of -C=N-, or C=N-N- function of Schiff base derivatives were capable of forming a coordination bonds with various metal ions, this property makes them versatile scaffold for complex compounds. Pyrroline analogues were synthesized from alkenes using chloramine-T as new reagent [27]. Benzothiazole based hydrazine Schiff base (**D**) has the ability to form the complexes of the type [Ru(2-((2-(benzo[d]thiazol-2-yl)hydrazineylidene)methyl)phenol)(CO)($AsPh_3$)$_2$] with Ru(II) metal ions. The complex can be used as catalysts in α-alkylation of aliphatic and aromatic ketones with alcohols. The complex was most efficient to get excellent yield, the catalytic system has a broad substrate scope, including mild reaction conditions, low catalyst loading under air atmosphere [28].



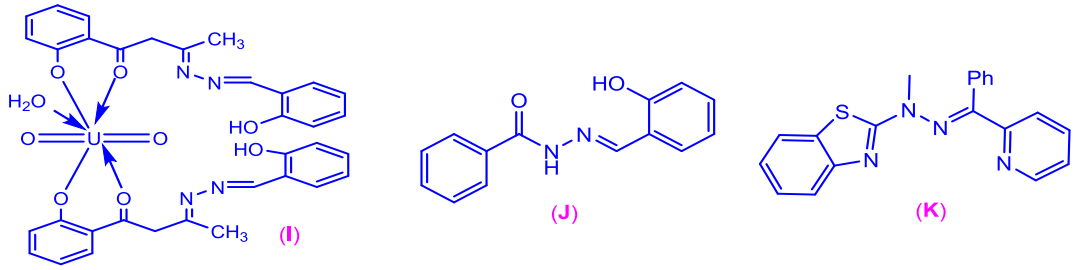
2-Aminoquinolin-3-yl phenyl hydrazone Schiff base (**E**) was useful for the detection of Al^{3+} metal ions colorimetrically [29]. The hydrazone displayed quick response to Al^{3+} with red shift of 34 nm at 427 nm in visible region over the other metal ions. Hydrazine Schiff bases are used as scaffolds in the synthesis of biologically active triazoles [30, 31], and 1,2,4-oxadiazoles [32] and thiadiazoles [33, 34]. The compound (*E*)-2-amino-*N*′-(1-(2-hydroxy-6-methyl-4-oxo-4*H*-pyran-3-yl)ethylidene)benzohydrazide (**F**) [35] acts as mono- and bidentate ligand to form complexes with Co(II), Ni(II), Cu(II) and Zn(II) metal ions, which displayed good anti-inflammatory activities. The Schiff base derived from 5-bromo-3-fluorosalicylaldehyde with 4,4'-diaminodiphenyl methane in the molar ratio 2:1 was more susceptible to form metal complexes with Cu(II), Ni(II) and Co(II) ions, which showed good antimicrobial activities [36].

The Schiff base (*E*)-*N*′-(2-hydroxybenzylidene)benzimidohydrazide (**G**) [37] was prepared by the reaction of 1-[3-(2-hydroxy benzylidene)amine)phenyl]ethanone and benzhydrazide in water without catalyst under an efficient environmental benign conditions, and was able to form mononuclear Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) complexes, and has photoluminescent properties. The study showed that ligand is coordinated to the metal ion through azomethine nitrogen and methaniminium nitrogen. The Schiff base (*E*)-*N*′-(pyridin-2-ylmethylene)benzo hydrazide (**H**) [38] form complexes with Cu(II), Ni(II) and Co(III) ions, which possess antibacterial activities against *E. coli*, *K. pneumonia*, *S. aureus*, *B. subtilis*. It has been reported in the literature that coumarin-hydrazine Schiff bases were efficiently transformed in to pyrazole derivatives through (3+2) annulation reactions, which displayed antimicrobial [39, 40], and antioxidant [41], activities. The Zn(II) and Cu(II) complexes of benzophenone benzoyl hydrazones and benzophenone salicylylhydrazones have the DNA interaction propensity with Herring sperm DNA with intercalation as the possible binding mode, wherein Cu(II) complex have greater binding strength than the other complexes [42].



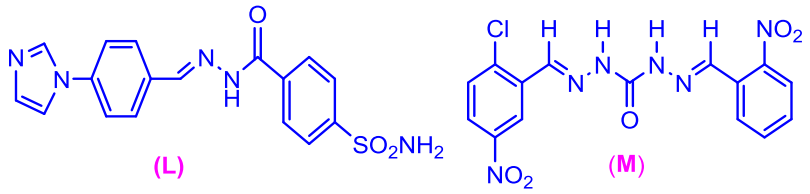
A polydentate Schiff base prepared from *o*-acetoacetylphenol with salicylaldehyde hydrazone forms mono- and binuclear complexes with Cr, Fe, Ni, Cu, Mn, Zn, Cd, Co, and U ions, of octahedral, tetrahedral and square-planar geometry, except the uranium complex which had seven-coordinate (**I**) [43]. The complexes displayed antimicrobial activity, and antitumor activity against HepG2 cell line. The tridentate Schiff base *N*-(2-hydroxybenzylideneamino) benzamide (**J**) [44] forms a metal complexes with Cu(II), and Ni(II) ions of antibacterial potencies. Further, results of binding studies with calf thymus DNA revealed a hyperchromic effect and a non-intercalative mode of binding, which indicate significant alterations of the bovine serum albumin.

A benzothiazole-pyridine hydrazone (**K**) [45] has displayed catalytic efficiency in Cu-TEMPO (2,2,6,6-tetramethyl-l-piperidinoxyl) aerobic oxidation of activated alcohols to form aldehydes with 100% selectivity, wherein the tridentate character of the ligand sacrifices some of the overall catalytic efficiency for the selectivity. In the complexes of Zn(II) and Eu(III) with bis-hydrazone, the ligand is doubly deprotonated incorporating two zinc(II) cores that are bridged with both phenolic group and acetate counter-ions [46]. The hydrazido-hydrazone Schiff base vanadium complexes showed the tyrosine phosphatases inhibition [47].

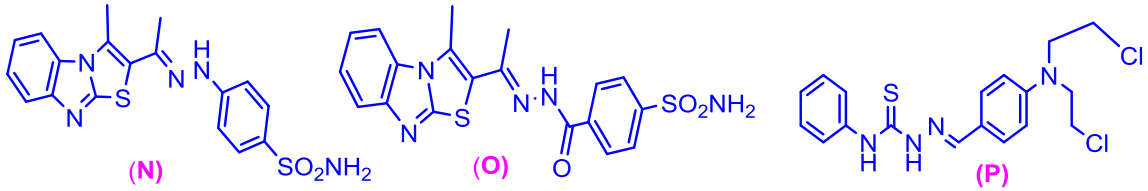


III. Biological Applications

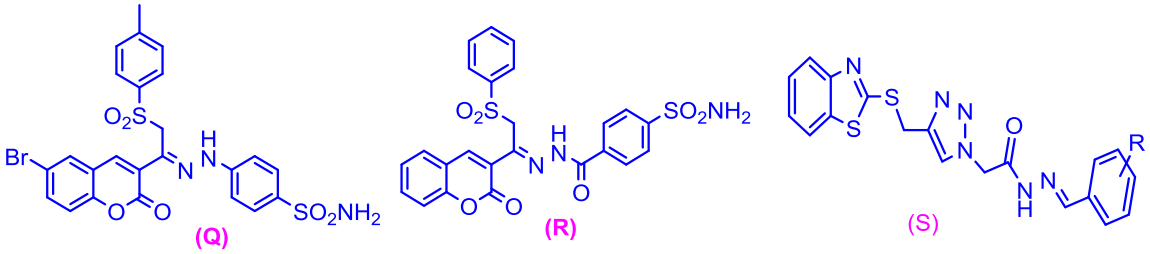
Discovery of carbonic anhydrase inhibitors is crucial for their clinical use as antiepileptic, diurectic and antiglaucoma agents. The sets of benzenesulfonamides incorporated with hydrophilic/hydrophobic tails by hydrazido or hydrazino linkers have inhibitory activity towards four human carbonic anhydrase isoforms with the K_I ranges: 76.8–357.4 nM (hCA I), 8.2–94.6 nM (hCA II), 2.0–46.3 nM (hCA XI), and 8.3–88.3 nM (hCA XII), of which the compound (**L**) [48] exhibited potent anti-proliferative activity against MCF-7 cell line under normoxic (IC_{50}: 3.32 ± 0.06μM) and hypoxic (IC_{50}: 8.53 ± 0.32 μM) conditions. The carbohydrazones possess *in vitro* carbonic anhydrase inhibitory potential, in which the compound (**M**) [49] of the series showed better inhibition (IC_{50} = 1.85 ± 0.24 μM) than the standard zonisamide (IC_{50} = 1.86 ± 0.03 μM).



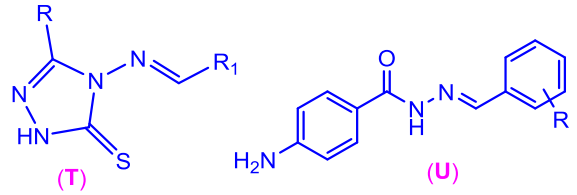
The 3-methylthiazolo[3,2-*a*]benzimidazole moiety connected to benzenesulfonamide *via* hydrazone (**N**), or hydrazide (**O**) linkers inhibit *h*CA I, II, IX and XII isoforms with good selectivity towards hCA IX over hCA I and II [50]. 4-[*Bis*(2-chloroethyl)amino]benzaldehyde-*N*-(4)-phenyl-thiosemicarbazone (**P**) [51] has showed cytotoxic effects on B16F10 melanoma cells (IC_{50} = 17.1 ± 3.1 μM) and A2058 cells.



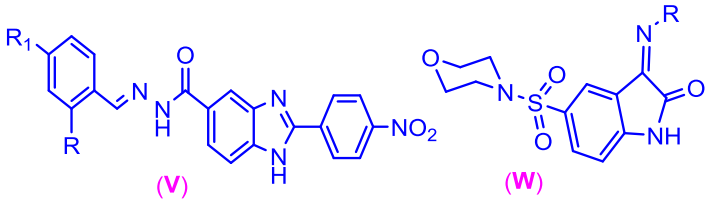
The benzenesulfonamide Schiff bases showed excellent inhibitory potency against physiologically relevant human carbonic anhydrases, hCA I, II, IX and XII as compared to clinically used drug acetazolamide [52]. The coumarin-sulfonamides emerged as non-selective CA inhibitors as they displayed good inhibitory activities toward hCA I, II, IX and XII isozymes. Notably, the "dual-tail" approach of compounds (**Q**) and (**R**) succeeded in achieving a good activity and selectivity toward CA IX/XII over the physiologically dominant CA I/II [53]. The range of anticancer drugs used in the treatment of colorectal cancer is small and is based mainly on systemic combination chemotherapy. 1,2,3-Triazole-benzothiazole-hydrazone Schiff bases (**S**) [54] showed anticancer activities against A549 and H1299 lung cancer cell lines. Schiff bases derived from the 5-hydrazino-3-methylisothiazole-4-carboxylic acid displayed antitumor potential, in which they have high selectivity towards leukemia and colon cancer cell lines, causing high inhibition of proliferation of MV4-11, and LoVo/DX [55].



Alpha-amylase and urease enzyme over expression endorses various complications like rheumatoid arthritis, urinary tract infection, colon cancer, metabolic disorder, cardiovascular risk, and chronic kidney disease. The arylhydrazide bearing Schiff base analogue found very active (IC_{50}: $0.8 \pm 0.05\mu M$) as compare to standard acarbose (IC_{50}: $1.70 \pm 0.10\,\mu M$) [56]. The *bis*-indolylmethane-hydrazone hybrids [57] demonstrated markable *β*-glucuronidase inhibitory potential with varying degrees in comparison with the standard D-saccharic acid-1,4-lactone. It interacted with amino acid residues located within the active site of *β*-glucuronidase enzyme. Schiff bases were regarded as useful synthons for the synthesis of biologically potent pyrroline derivatives [58]. Coumarin based hydrazone Schiff bases exhibited remarkable α-glucosidase inhibitory potential with IC_{50} values between 1.10 ± 0.01 - $36.46 \pm 0.70\,\mu M$ comparable with acarbose ($IC_{50} = 39.45 \pm 0.10\,\mu M$) [59]. The structure activity relationship was mainly based upon by bring about difference of substituents on phenyl part. Resistance to β-lactam antibiotics producing metallo-β-lactamases represents a major medical threat and there is urgent need to develop clinically useful inhibitors. A number of 4-amino-1,2,4-triazole-3-thione-derived Schiff bases (**T**) [60] inhibited metallo-β-lactamases L1, VIM-4, VIM-2, IMP-1, with K_i values in the μM to sub-μM range. (*E*)-4-Amino-*N*′-(substituted benzylidene) benzohydrazides (**U**) [61] have markable antimicrobial activities against the tested organism, notably, the electron donating and withdrawing groups played important roles activities of these compounds. The hydrazine Schiff bases efficiently undergo 1,3-dipolar cycloaddition reactions to produce pyrazole derivatives of potent antimicrobial activities [62-64].



The inhibition of chitinase activity is considered of great importance for the development of novel antifungal agents. The 4-hydoxycoumarin with Schiff base motif displayed promising inhibition effect against phytopathogenic fungi, *F. solani*, *F. oxysporium*, *A. niger* and candida species *C. krusei*, *C. albicans*, *C. tropicalis*. The Schiff's bases displayed the highest chitinase inhibition effects ($IC_{50} = 1.0$ mM) comparable with previous reports [65]. The benzimidazole hydrazone derivatives (**V**) [66] possess antimicrobial activities *C. albicans* and *C. neoformans* with MIC values of 4-16 μg/mL, and were not cytotoxic against red blood and human embryonic kidney cells. Fused pyrazoles [67] and pyrazole integrated 1,3,4-oxadiazoles [68] derived from hydrazine Schiff bases possess potential antimicrobial activities. The Schiff bases (**W**) have significant antimicrobial activities, and inhibitory effect against DNA gyrase isolated from *S. aureus* [69].



The current drugs used for the treatment of inflammation were unable to cure effectively, more importantly are associated with side effects. 1,2,4-Triazole Schiff bases (**X**) [70] effectively deal with such diseases by inhibiting COX-1 and COX-2. The results of *in vivo* assays tested by carrageenan-induced mice paw edema against albino mice shows 15.8% inhibition after 1 h with respect to the standard drug. The pyrazolopyrimidine Schiff base analogues (**Y**) [71] have displayed higher anti-inflammatory activities and were found safer than indomethacin. Discovery of multifunctional agents for the treatment of Alzheimer's disease (AD) is an attractive therapeutic approach, and β-site amyloid precursor protein cleaving enzyme 1 (BACE1) inhibitors with desirable blood brain barrier permeability play a pivotal role in treating. The quinazolinone-hydrazone derivatives acts as new multi-target candidates for the treatment of AD, of which compound (**Z**) [72] showed the highest activity with an IC_{50} value of 3.7 μM against BACE1, and therefore is a lead for the non-peptidic BACE1 inhibitors. The hydrazone Schiff bases were efficiently transformed in to fused pyrans [73], 1,2,4-oxadiazoles [74] and coumarin tethered 1,3-oxadiazines [75], which showed promising antimicrobial and antioxidant activities; and pyrazole derivatives having anti-inflammatory and antimicrobial activities [76, 77].

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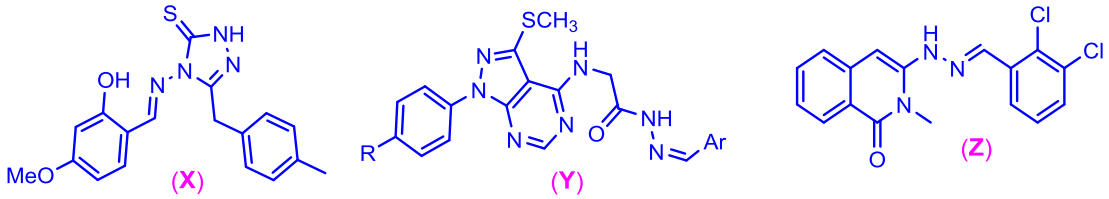
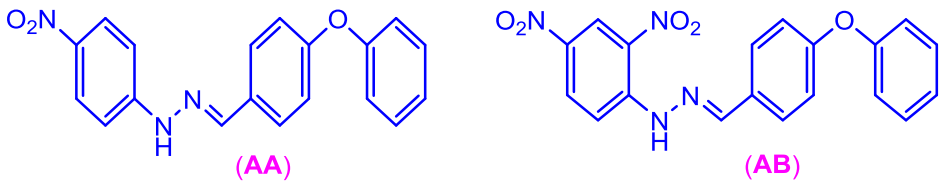


IV. Physico-Chemical Properties

It has been reported in the literature that, Schiff base and their derivatives exhibit various physical properties. For instance, 1-(4-nitrophenyl)-2-(4-phenoxybenzylidene)hydrazone (**AA**) and 1-(2,4-dinitrophenyl)-2-(4-phenoxybenzylidene)hydrazone (**AB**) [78] displayed electronic, optical and positive solvatochromism, solute-solvent interaction properties and were act as insulator unuder applied electric field. The molecular electrostatic potential surface of the 5-chlorosalicylaldehyde-2,4-dinitrophenylhydrazone shows that, the oxygen of nitro group are prone to electrophilic attack and the hydrogen of hydrazine group is prone to nucleophilic attack [79]. The tetradentate Schiff base prepared from 2-aminobenzaldehyde with o-phenylenediamine form complex with Cu(II) ions, which prefer to bind to DNA in Cu(II) rather than Cu(I) state [80].



The compounds 2-[(2*E*)-2-(2-chloro-6-fluorobenzylidene)hydrazinyl]pyridine [81] has (*E*)-1-(2,3-dichlorobenzylidene)-2-phenylhydrazine [82], and (*E*)-2-(1-(2-phenylhydrazono)ethyl)phenol [83] displayed non-linear optical properties. The Schiff base derived from 2, 4-dinitrophenylhydrazine and benzaldehyde exhibited inter-contact interactions [84]. The chromene conjugated Schiff bases have shown anti-corrosion efficiencies for carbon steel in a 15% HCl environment, and have cathodic effect, they form a protective film on the steel surface, causing a reduction in the surface adsorption of Cl^- on the metal substrate [85]. A sulfamethoxazole Schiff base (*E*)-4-(4-methoxybenzylideneamino)-*N*-(5-methylis-oxazol-3-yl) benzenesulfonamide form copper complex showed good thermal stability [86].

V. Conclusion

The organic compounds, particularly, the Schiff base derived by the reaction of carbonyl compounds and amines were regarded as useful scaffolds for the synthesis of compounds of diverse applications. The synthetic structure and structural optimization is promising area for potential drug discovery and development. The present review concluded on the developments in the area of synthetic strategies of Schiff bases, their utility as building blocks, medicinal perspectives, and also describes their structure-activity relationships studies. The discussion on the physical properties, like electronic, optical and positive solvatochromism, solute-solvent interaction, anti-corrosion properties, exploration of chemical reactivity of Schiff base derivatives in this review might be useful for the researchers working in this area all over.

CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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