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REVIEW ARTICLE

Review: Schiff base metal complexes as anti-inflammatory agents

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ABSTRACT

Schiff bases (SB) have unique potential to bind metal ions for widespread applications, especially in the pharmacological industry. The condensation of primary imine and carbonyl compounds produces SB where azomethine functional group appears as a result of replacement of carbonyl group by imine group. A tetradentate salen type SB ligand is a famous unsymmetrical bifunctional ligand that plays a major role in industrial and biological activities. The complexation of SB ligand with copper, zinc, cobalt, nickel, aluminum, ruthenium, vanadium, etc. produce a variety of useful metal complexes. SB and their metal complexes exhibit excellent biological activity for anti-malarial, anti-viral, anti-tumor, anti-fungal and anti-inflammatory properties. This review highlights the current state of knowledge on SB metal complexes with spotlight on synthesis of various SB ligands, metal complexation and their role as anti-inflammatory drugs. Inflammation is generally considered as response of the immune system against burns, allergens and toxic chemicals. Anti-inflammatory and analgesic activity of various SB complexes in different classes of mice and rats have been described by using carrageenan induced edema. The diverse SB metal complexes reported especially in the last two decades are comprehensively reviewed in order to evaluate their suitability as anti-inflammatory and analgesic agents.

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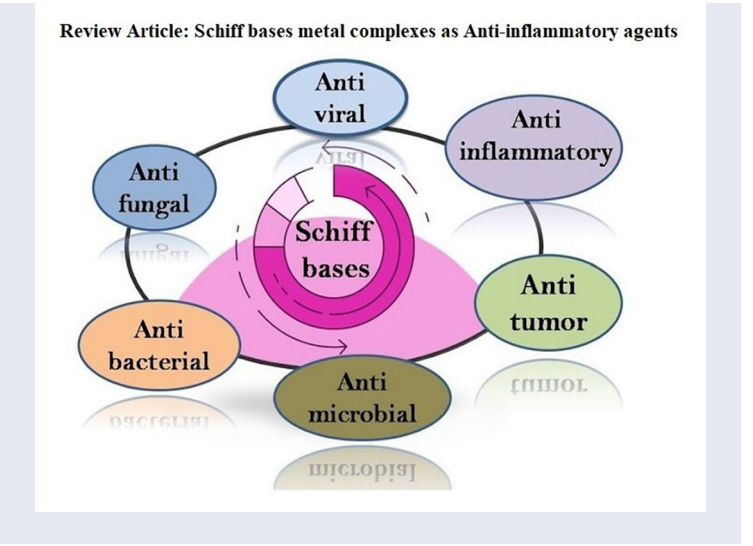


1. Introduction

Every fourth human in the world will face an inflammatory disease. The inflammation is natural response of our innate immune system leading to protective process against illness and injuries. Inflammations are basically classified into acute and chronic types. The acute inflammation involves lesser extent of infections whereas the chronic inflammation involves a variety of diseases, including cardiovascular diseases and type two diabetes. The current clinical treatment to cure inflammations involves use of steroidal or non-steroidal drugs based on a number of chemical structures. Considering the current status as well as emergence of new inflammatory diseases, Schiff base ligands and related metal complexes are worthwhile to study. The properties of the ligands and their metal complexes applicable to cure inflammations reported during the last two decades are comprehensively described in the following sections.

Ligands are building blocks in coordination chemistry, acting as functional groups that bind to metal ions to produce complexes. Generally, ligands are donor atoms that donate pairs of electrons to the metal ion, behaving as Lewis bases. Ligands like nalidixic acid, cinoxacin, 2-guanidinobenzimidazole and N-carboxymethylpseudoephedrine provide electrons towards central metal ion and show biological activities [1]. Schiff bases (SB) were discovered in 1864 by Hugo Schiff by a condensation process. Schiff bases are the condensation product of carbonyl compounds, including aldehydes/ketones and primary amines as shown in Figure 1 [3, 4]. SB, comprising an imine or azomethine functional group (–C = N–), are utilized in the development of other compounds.

The SB is classified into several groups, salen type ligands, salophen type ligands, hydrazone type ligands and semicarbazones/thiosemicarbazones.

Salen type ligands and their derivatives were identified in 1933 on the basis of their complexing abilities, catalysis, bioinorganic chemistry and magnetism [5]. These ligands are prepared by the reaction of ethylenediamine and salicylaldehyde as shown

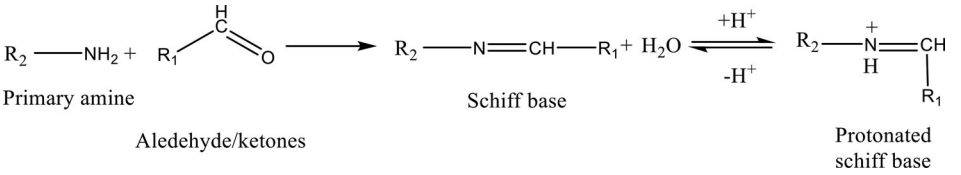


Figure 1. Preparation of Schiff base by condensation of primary amines and carbonyl compounds [2].

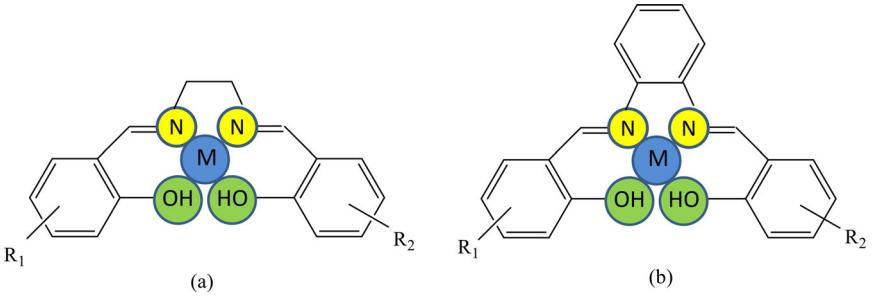


Figure 2. Structures of salen (a) and salophen (b) type ligands [5].

in Figure 2(a). The central metal ions and ligand backbone in salen type ligands can vary in order to make it useful in various biological and industrial applications.

The salophen ligands are considered as the most ancient class of compounds in coordination chemistry [5]. These tetradentate ligands are formed by condensation of salicylaldehyde and *o*-phenylenediamine as shown in Figure 2(b). The metal complexes of salophen type ligands have been important as candidates for several medical and industrial applications [6].

Hydrazone ligands are synthesized by reaction of aldehydes and ketones (carbonyl compounds) with hydrazine [5]. The acyl hydrazone and aroylhydrazone are two subclasses of hydrazone type ligands. The hydrazone ligands possessing only one donating atom are unidentate ligands but their sub groups contain two donating atoms as bidentate ligands. The hydrazones play a major role in selectivity of drug candidates.

These ligands appeared in 1800 and later proved as good chelating agents [5]. Semicarbazones/thiosemicarbazones have been prepared by condensation of carbonyl compounds and semicarbazide or thiosemicarbazide. Semicarbazones/thiosemicarbazones have various donor atoms and are tridentate. These ligands are important because of their lipophilic nature and chelating ability.

There is no specified selection criterion to include the synthesis techniques in the coming sections. The general description of the methods utilized to synthesize SB complexes is provided to give a bird's eye view. However, commonly used methods, when economy and ease are considered, are described in some detail in Section 2.

2. Schiff base ligands

There have been a variety of SB ligands synthesized using different techniques, described below.

2.1. Phthalimide Schiff bases

The heterocyclic and homocyclic phthalimide Schiff bases have been derived by condensation of pyridine-2,3-dicarboxylic anhydride by *p*-phenylenediamine and phthalic anhydride with carbonyl compounds. The combination of Schiff base complexes with heterocyclic components has exhibited a wide range of medicinal importance in anti-fungal, anti-viral and anti-bacterial agents [5]. Phthalimides have demonstrated great pharmaceutical activity against Parkinson's disease and anti-inflammatory responses [7].

2.2. Salicylaldehyde-sulfamerazine ligand

The sulfamerazine-salicylaldehyde ligands are the best anti-microbial agents synthesized by mixture of salicylaldehyde and sulfamerazine in the presence of methanol [8]. Panneerselvam *et al.* used themorpholine and 4-chloronitrobenzene to synthesize 4-(4-nitrophenyl)-morpholine that is reduced further to 4-aminophenyl-morpholine by condensing it with aldehyde. The resulting Schiff base, 4-(4-aminophenyl)-morpholine, is used as an antimicrobial agent [9]. 2′-Amino-4′-(6-bromo-3-coumarinyl)thiazole has been synthesized by cyclization of 3-bromoacetyl-6-bromocoumarin with thiourea in the presence of piperidine catalyst to produce the Schiff base aminothiazolylbromocoumarin [10]. This Schiff base has been synthesized using three ways: reflux method, heating by conventional method and microwave-induced organic reaction enhancement (MORE). The third way has produced better yield of Schiff bases used in antibacterial activity.

Schiff bases have been synthesized by condensation of carbonyl compound with primary amine under azeotropic distillation [11]. Molecular sieves were used to prevent hydrolysis of the amine bond. Chakraborty *et al.* found that efficiency of these methods depends on strong electrophilic carbonyl compounds and nucleophilic amines [12]. The authors used Lewis acids such as $NaHCO_3$ and $Mg(ClO_4)_2$ for activation of aldehydes, catalyzing the nucleophilic attack and removing water in products. Among the various techniques for production of Schiff bases, microwave irradiation has been widely used because of its enhanced yield and high selectivity within limited time periods.

Prior to synthesis of the final product, the authors prepared precursor solutions 1-{[2-(1H-Indol-3-yl)-ethylimino]methyl}-naphthalen-2-ol by reaction of 2-hydroxy-naphthalene-1-carbaldehyde (0.01 mmol) and 2-(1H-indol-3-yl)-ethylamine (mmol) in ethanol solution. The synthesized mixture was allowed to reflux and recrystallized from ethanol. Afterwards, the Schiff base 1-[(2-{1-[(dicyclohexylamino)-methyl]-1H-indol-3-yl}-ethylimino)-methyl]naphthalen-2-ol (HL) was mixed with dicyclohexyl amine and formaldehyde. The mixture was refrigerated and then the crude product recrystallized [13]. Raman *et al.* prepared a Schiff base 4-aminoantipyrine by mixing 3-hydroxy-4-nitrobenzaldehyde in ethanol with *o*-phenylenediamine under reflux [14]. The mixture was allowed to recrystallize and pure yellow solid Schiff base was obtained. The resultant Schiff base has applications in clinical, biological, pharmacological and analytical areas.

2.3. Macrocyclic Schiff base

A precursor for formation of macrocyclic Schiff base has been prepared by addition of salicylaldehyde, ethanolic KOH and 1,2-dibromoethane under reflux [15]. The Schiff base 1,4-bis(ethylamino)anthraquinone was prepared by heating ethylenediamine, bisaldehyde and ethanol. A solid mass was recrystallized and pure yellow ligand obtained. The collected Schiff base has been used for anti-fungal and anti-bacterial activities. 2,3-Diaminopyridine (DAPY) and aldehydes, salicylaldehyde (SalH), 4-hydroxybenzaldehyde (4-OHBenz) and 4-nitrobenzaldehyde (4-NO_2Benz) have been utilized to prepare Schiff bases [16]. A mixed Schiff base, DAPY-{4-OHBenz}{SalH}, has also been synthesized and the products were investigated using NMR and magnetic susceptibility measurements. The prepared Schiff bases have been transformed into metal complexes using nickel(II), zinc(II) and copper(II) for studying the antibacterial characters.

2,6-Pyridinedicarboxaldehyde bis(*o*-hydroxyphenylimine) is synthesized from mixture of 2,6-pyridinedicarboxaldehyde, 2-aminophenol and ethanol [17]. The yellow precipitates of pure ligand gave 85% yield. The synthesized ligand had activity against bacterial species. A Schiff base ligand has been prepared by addition of salicylaldehyde to solution of 2,2′-bi(p-methoxyphenylamine) in ethanol under reflux; pure white crystals were formed in 94% yield.

Schiff base metal complexes have been prepared by addition of Co, Mn, Cu and ligand with ethanol under reflux by recrystallizing the product. In 2020, Han *et al.* synthesized N'^4-bis(2-hydroxy-5-nitrobenzylidene)succinohydrazide from mixture of 5-nitrosalicylaldehyde, HCl and solution of succinic dihydrazide in ethanol under reflux [18]. The ligand as a yellow solid was obtained in 73% yield. Omidi *et al.* reviewed the research efforts for Schiff base hydrazones and oxime derivatives of curcumin [19].

2.4. Curcumin ligand

The synthesis of curcumin aniline as nanoparticles has been carried out using green synthesis. The functionalized nanoparticles were effective antimicrobial agents. Another preparation of new curcumin-based ligand has been reported by Kareem *et al.* [20]. The reaction of nicotinamide and curcumin produced bidentate ligand which forms complexes with Co, Ni and Cu with 1,10-phenanthroline [19]. The synthesized metal complexes show good antibacterial activity. Condensation of hydroxyaldehydes and diamines in the presence of ethanol has provided pure tetradentate Schiff base that was recrystallized from dichloromethane and hexane through evaporation [21]. The diacylhydrazone Schiff base has been synthesized by condensation including succinic dihydrazide and nitrosalicylaldehyde and investigated with fluorescence and ultraviolet spectroscopy [18]. A series of Schiff bases have been synthesized by reaction of benzoxazole or benzimidazole with 9-aminoacridine. Condensation of diamines with 2-hydroxynaphthaldehyde has been involved in formation of Schiff bases [2], which were screened for anti-inflammatory and analgesic activity. Condensation of diamines and amines with 3-isothiocyanatobutanal and 4-isothiocyanato-4-methyl pentan-2-one produced compounds screened for analgesic and anti-inflammatory activity [22].

2.5. Quinoline Schiff base

Cyclotriphosphazene with quinoline Schiff base has been synthesized by nucleophilic substitution reaction and was characterized by using mass spectrometry, elemental analysis and FTIR spectroscopy [23]. The Schiff base has been screened against anti-mycobacterial, anti-microbial, anti-hypertensive and anti-cancer activity.

2.6. Quinazolinone Schiff base

Quinazolinone-based Schiff base has been prepared and examined for anti-inflammatory and antioxidant activity. The antioxidant activities have been compared with other antioxidants, gallic acid and ascorbic acid. These compounds have revealed exceptional anti-inflammatory activities [24]. Antioxidant activity has been explained as radical scavenging activity of phenolic Schiff base by Anouar *et al.* [25].

2.7. Sulpha drug Schiff base

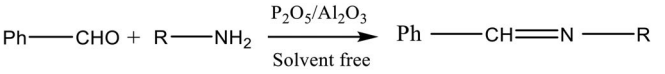
Krátký *et al.* synthesized 4-[(2-hydroxybenzylidene)amino]-*N*-m (pyrimidin-2-yl)benzenesulfonamides [26], a Schiff base derived from sulfadiazine and salicylaldehyde. The compound was screened against anti-microbial, anti-fungal and anti-bacterial activities [26]. A Schiff base has been synthesized by condensation of 2-amino-4-methylthiazole with 4,6-diacetyl resorcinol; their electronic and structural properties have been studied by IR spectra, H-NMR, and thermal analysis [27].

3. Synthesis of Schiff bases

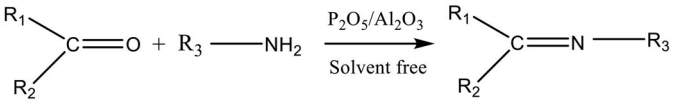
There are several schemes for synthesis of Schiff bases, out of which suitable ones may be adopted by considering availability of precursors, environment and requirements. The basic scheme is comprised of treatment of aldehyde compound (e.g. benzaldehyde) with an aromatic or aliphatic amine in the presence of catalyst (e.g. P_2O_5 supported on Al_2O_3) without involving any solvent as shown in Figure 3. Another scheme may consist of treating carbonyl compounds and mono amines using a suitable catalyst (say e.g. P_2O_5 supported Al_2O_3) at elevated temperatures in solvent free environment, as given in Figure 3 [28].

The reaction of diamines with 2-hydroxyacetophenone in the absence of any catalyst produced Schiff bases that further synthesized double Schiff bases under reflux. The double Schiff bases were of high yield within short reaction time. The new Schiff bases are prepared by recrystallization of mixture of benzaldehyde, isopropyl amine, methanol and P_2O_5/Al_2O_3 as a catalyst in the absence of solvent as shown in Figure 3 [28]. Double Schiff bases have been synthesized by recrystallization of mixture of salicylaldehyde, diamine, methanol and P_2O_5/Al_2O_3 as a catalyst in the absence of any solvent. The description and properties of different reported SB are described in Table S1.

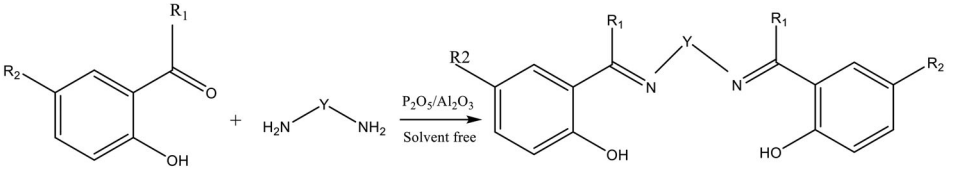
The Schiff base 2-amino-5-aryl-1,3,4-thiadiazole has been fabricated by recrystallization of mixture of aldehyde, 2-amino-5-aryl-1,3,4-thiadiazole and alcohol under reflux.



Scheme 01



Scheme 02



Scheme 03

Figure 3. Synthesis of Schiff bases by reaction of carbonyl compounds with various diamines in the presence of catalyst P_2O_5/Al_2O_3, shown in schemes 1, 2 and 3 [28].

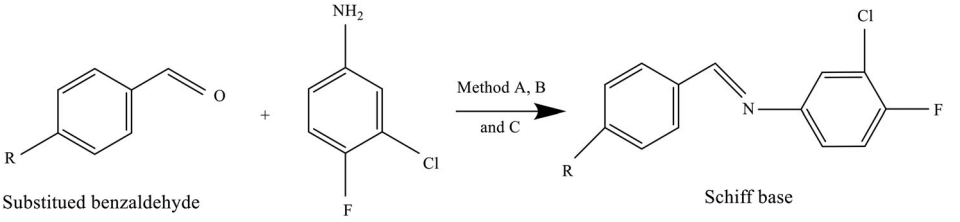


Figure 4. Synthesis of Schiff bases from benzaldehyde and amine (3-chloro-4-fluoroaniline) using green method [29].

The Schiff base naphtha[1,2-d]thiazol-2-amine has been prepared by mixture of aromatic aldehyde, glacial acetic acid under reflux and recrystallization [28].

3.1. Green method

Green methods of synthesis used for preparation of Schiff bases have achieved high yield per the following scheme [29]. In water-based green method, exothermic reaction of aldehyde (e.g. benzaldehydes) and amine (e.g. 3-chloro-4-fluoro aniline) produces fine crystalline product in high yield as shown in Figure 4. In the microwave jump start method, the mixture of aldehyde (e.g. benzaldehydes) and amine (e.g. 3-chloro-4-fluoroaniline) in the presence of enzyme (e.g. piperidine) is microwave irradiated to produce good yield of Schiff base.

Another green method for synthesis of Schiff base is the grindstone "friction activated" method in which mixture of aldehyde (e.g. benzaldehydes) and amine (e.g. 3-chloro-4-fluoroaniline) are ground to produce pure crystals of Schiff base.

3.2. Microwave irradiation method

Yang *et al.* used 3,4,5-trimethoxybenzaldehyde as precursor and *p*-toluidine for synthesis of (*E*)-4-methyl-N-(3,4,5-trimethoxybenzylidene)benzenamine SB using three different routes [30]. First, they irradiated mixture of 3,4,5-trimethoxybenzaldehyde, *p*-toluidine, dichloromethane and neutral ammonia in a microwave oven to obtain a product which was recrystallized using petroleum and ethyl acetate to obtain 85% pure desired Schiff base.

3.3. Reflux method

Second, the solution of precursor, benzene and *p*-toluidine was heated under reflux to crystallize the material to obtain 72% pure product as white lamellar crystal.

3.4. Rotary evaporation method/conventional heating method

Third, solution containing precursor, DCM and $MgSO_4$ to obtain a filtrate has been dissolved in heated ethanol and hot water. The solution crystallized giving 75% product in white crystalline form. Comparison indicated potential of the first method to utilize microwave irradiation for production of clean and cost-effective Schiff base at high yield for industrial purposes.

4. Schiff base metal complexes (coordination complexes)

Coordination complexes are formed by combining Schiff bases with transition metals (Table 1) such as cobalt, copper, manganese, vanadium and ruthenium [35]. Zinc(II) complex synthesized by *in-vitro* human blood cell stabilization method (HRBC) exhibits better anti-inflammatory activity in comparison with Diclofenac, a widely used drug [36]. Suryawanshi, suggested that some transition metals are used as anti-inflammatory agents like oxadiazole and copper bracelets used in treatment of rheumatoids [37].

4.1. Mannich complexes

Schiff base Mannich complexes have been prepared by reaction of metal salts like $VOSO_4{\cdot}H_2O$, $MnCl_2{\cdot}4H_2O$, $CrCl_3{\cdot}6H_2O$ and $FeCl_3{\cdot}2H_2O$ to the ligand and the mixture allowed to recrystallize [13]. The complexes have different geometries, octahedral for Cr(III) and Fe(III), tetrahedral for Mn(II), Cd(II), and Hg(II) and square planar for Pd(II). The authors carried out detailed analyses of biological activities of the complexes and found them active in antimicrobial applications.

Wilkinson *et al.* prepared a Schiff base metal complex in two steps [31]. First, Schiff base (SB) has been prepared by addition of benzhydrazide in water and salicylaldehyde in ethanol separately then mixing them with continuous stirring. Second, SB and Cu^{2+} or Fe^{3+} were mixed on a steam bath in the presence of ethanol for synthesis of Schiff base metal complex. The metal SB complex was collected in solid form and characterized using UV-Visible spectroscopy in order to calculate the yield. The Schiff

Table 1. Schiff base and metal complexes showing their appearance, yield and precursors.

Coordination compounds	Precursors	Appearance	Yield	Melting point	Reference
4-(4-(Furfuryl-imino)-phenyl)-morpholine 5	N-A	N-A	59%	N-A	[14]
4-(4-(2-Hydroxybenzylidene-imino)-phenyl)-morpholine 6	N-A	N-A	85%	N-A	
$[Mn(L)(H_2O)_2]Cl$	N-A	Light yellow	69%	232 °C	[17]
$[Pd(L)(H_2O)_2]Cl$	N-A	Red brown	60%	210 °C	
$[Cd(L)(H_2O)_2]Cl$	N-A	Light brown	81%	194 °C	
$[Cu(4\text{-Aminoantipyrine})Cl_2]$	N-A	Dark brown	56%	N-A	[18]
$[VO(4\text{-Aminoantipyrine})Cl_2]$	N-A	Green	56%	N-A	
$[Cd(4\text{-Aminoantipyrine})Cl_2]$	N-A	Yellow	59%	N-A	
$[Ni(DAPY\text{-}(NaphH\}z)_2]$	Nickel, DAPY, ethanol and 2-hydroxy-1-naphthaldehyde	Red	>250	67%	[31]
$[Cu(DAPY\text{-}(NaphH\}z)_2]$	Copper, DAPY, ethanol and 2-hydroxy-1-naphthaldehyde	Brown	>250	54%	
[Cu(MeONS)Br]	Copper(II) bromide complex, hydrazine hydrate, 2-methoxybenzaldehyde, potassium hydroxide, and benzylchloride	Reddish green	N-A	N-A	[32]
$C_{32}H_{22}N_6O_2Cu$	N-A	Red	78%	N-A	[33]
$C_{32}H_{22}N_6O_2Ni$	N-A	Red	76%	N-A	
$C_{32}H_{22}N_6O_2Zn$	N-A	Yellow	68%	N-A	
$[Fe((E)\text{-}2\text{-}(((3\text{-aminophenyl})imino)methyl)phenol)(H_2O)Cl_2]Cl\cdot H_2O$	Iron(II) aquo (E)-2-(((3-aminophenyl)imino)-methyl)phenol complex	Black solid	62.9%	121 °C	[34]
$[Co((E)\text{-}2\text{-}(((3\text{-aminophenyl})imino)methyl)phenol)(H_2O)Cl_2]\cdot H_2O$	Cobalt(II) aquo (E)-2-(((3-aminophenyl)-imino)methyl)phenol complex	Blue solid	84%	120 °C	

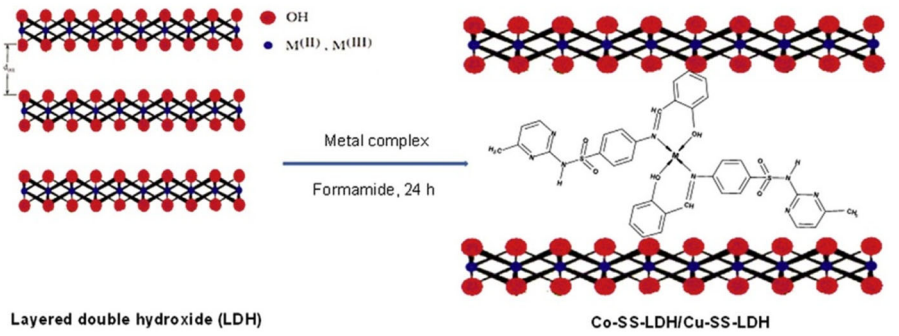


Figure 5. Formation of metal complexes with layered double hydroxides *via* intercalation. Reprinted with permission from reference [8] Copyright 2019, open access, Elsevier.

base metal complexes are of biological importance such as anti-inflammatory, anti-oxidant, anti-bacterial, anti-fungal and anti-tumor.

4.2. Sulfamerazine Schiff base complexes

The synthesis of salicylaldehyde-sulfamerazine (SS) ligand was given in the section on Schiff base ligand synthesis. Complexation of copper and cobalt with SS has resulted in sulfamerazine SB complex. Co(II) and Cu(II) sulfamerazine complexes have shown anti-microbial and anti-bacterial activities (Figure 5) [8].

Coordination complexes have also been synthesized by addition of 2-(2′-hydroxy)-benzylidene amino naphtha thiazole to Ni(II), Co(II) and Cu(II) under reflux [32]. The complexes were re-precipitated and allowed to dry in vacuum. Detailed analysis showed that these metal complexes have anti-bacterial activities; properties of different metal complexes are listed in Table S1.

The synthesis of mono-condensed 2,3-diaminopyridine (DAPY) pyrrole-2-carboxaldehyde (DAPY-{Pyrr}) Schiff base and bis-condensed 2,3-diaminopyridine 2-hydroxy-1-naphthaldehyde (DAPY-(NaphH}z) have been prepared by mixing DAPY with pyrrole-2-carboxaldehyde and 2-hydroxy-1-naphthaldehyde in ethanol, respectively [33]. The coordination complexes were investigated using IR spectra and NMR spectra to get insight into the structures of the compounds. Magnetic measurements of these compounds were also studied which indicated that nickel, iron and zinc complexes were diamagnetic in nature. These SB and their metal complexes were used against antibacterial diseases. The S-benzyl-β-N-(2-hydroxyphenyl)methylenmonopyridine-nickel(II) complex has been prepared by crystallization of mixture of S-benzyl-β-N-(2-hydroxyphenyl)methylendithiocarbazate (ligand) with nickel(II) nitrate hexahydrate and pyridine [34]. The precursors and properties of some reported metal complexes are listed in Table 1.

Schiff base 4-(benzeneazo) salicylaldehyde was prepared from aniline, hydrochloric acid, salicylaldehyde and anhydrous sodium carbonate under reflux [38]. The metal complexes were synthesized by reaction of $Cu(CH_3COO)_2{\cdot}H_2O$, $Co(CH_3COO)_2{\cdot}4H_2O$, $Ni(CH_3COO)_2{\cdot}4H_2O$ and $Mn(CH_3COO)_2{\cdot}4H_2O$ and 4-(benzeneazo) salicylaldehyde in refluxing ethanol. The authors suggested that the metals bind to ligand by phenolic

oxygen and imino nitrogen. The appearance and yield values of different metal complexes are listed in Table S1.

El-Sonbati *et al.* synthesized coordination complexes by addition of (E)-2-(((3-aminophenyl)imino)methyl)phenol to Zn(II), Cd(II), Ni(II) and Mn(II) in ethanol under reflux [39]. The mixture was filtered and recrystallized to obtained pure complex in 70% yield. The authors indicated that the metal complexes show more antimicrobial activity than ligand. Metal complexes have been synthesized by addition of metals (Cu, Co, Mn, VO) to 4-aminoantipyrine in refluxing ethanol [14]. The solid complex formed was filtered to collect metal complexes. The detailed biological analysis suggested that Ni, Co and Cu complexes cleave DNA by redox chemistry.

Coordination complexes have also been prepared by addition of 1,4-bis(ethylamino)anthraquinone to Co, Ni, Cu and Zn and then allowed to crystallize [16]. Spectroscopic studies indicated that the complexes have octahedral geometries. These complexes were characterized for anti-fungal and antibacterial activities. Schiff base complexes were synthesized by mixture of metal bromide and chloride salts with 2,6-pyridinedicarboxaldehyde bis (*o*-hydroxyphenylimine) under reflux [17]. The complexes were screened for antibacterial activity.

The basic precursor for synthesis of a hexadentate ligand has been prepared by aerial oxidation of 2-aminothiophenol [40]. The hexadentate ligand was synthesized by condensation of salicylaldehyde with 2,2′-disulfanediyldianiline in methanol. The purity of these Schiff bases was determined by elemental analyses. The prepared ligands reacted with nickel nitrate to give complexes characterized by NMR spectroscopy and absorption and emission spectroscopy. The complexes were used for sensing of chemophosphates. Another complex was synthesized by condensation of 2,2′-disulfanediyldianiline with thiophene-2-carboxaldehyde in ethanol [41]. These complexes had antimicrobial activities.

Coordination complexes were prepared by addition of (N'^4-bis(2-hydroxy-5-nitrobenzylidene)succinohydrazide) with Cd, Zn and Eu with NaOH in methanol [18]. The ligand showed no interaction with monovalent metal ions and reacted immediately with divalent and trivalent metals. These studies were carried out by using UV visible and fluorescence spectroscopy.

4.3. Other Schiff base complexes

SB metal complexes have been prepared using condensation of ligand with Co(II), Cu(II), Cr(II), Fe(II) and Cd(II). These complexes have played a role in anti-cancer and anti-bacterial activities [27].

4.4. Nophen Schiff base complexes

The synthesis of Nophen SB [N,N-bis(2-hydroxy-1-naphthaldehyde)-o-phenylenediamine] and the Co(II)-Nophen complex and characterization by fluorescence, cycloltametricric and UV-visible techniques have been reported [42]. The negative peak in cyclic voltammetry showed electrostatic interaction that revealed that Co(II)-Nophen complex has significant response when compared with bare Nophen.

4.5. Chiral Schiff base complexes

Chiral SB metal complexes have been synthesized by addition of salicylaldehydes and 1,2-diaminocyclohexane or 2,2′-diamino-1,1′-binaphthalene with nickel, zinc, copper, manganese or cobalt [43]. The complexes have been characterized using ^{1}H and ^{13}C NMR and chiral complexes containing manganese have been obtained by oxygenation. The copper-based Schiff base complex of quinoline-2-carboxaldehyde with biological activities of anticancer, antipyretic, antimicrobial and anti-inflammatory properties have been reported [44]. The mononuclear cobalt complex has been synthesized from quinoxaline-2-carboxalidine, 2-amino-5-methylphenol and studied *via* UV-Visible spectroscopy, X-ray diffraction, elemental analysis, IR, conductivity and TGTDA [45]. Cobalt has distorted octahedral geometry with Schiff base in *cis* arrangement.

The reaction of 1,2-di(o-aminophenylthio)ethane and 3-ethoxy-2-hydroxybenzaldehyde yielded thioether ligand which produced Schiff base metal complexes on reaction with Ni(II), Cd(II), Zn(II) and Hg(II). The nickel-based complexes have been characterized by X-ray crystallography [46]. Cd(II), Zn(II) and Hg(II) complexes have been investigated by molar conductivity and UV-Visible spectroscopy.

4.6. Magnesium-based Schiff base complexes

Mg coordination complexes have been synthesized by reaction of tridentate ligand and magnesium metal in the presence of toluene [47]. The characterization showed that compounds have crystallized as five-coordinate dimers having magnesium bonded to oxygen atoms of benzyl alkoxides and the reactivity has been disturbed by electronic effect of substituents on ligand.

4.7. Ruthenium-based Schiff base complexes

Ru-based SB complexes have been formed by treatment of a SB and ruthenium which exhibited sensitivity and catalytic activities in protic solvents [48]. SB complexes were synthesized by condensation –f -(diethylamino)-salicylaldehyde and diaminomaleonitrile in the presence of nickel metal. The process formed a nickel amido bond by deprotonation of primary amine and raised possibility for a new molecular switch [49].

4.8. Curcumin-based Schiff base complexes

Such coordination complexes are synthesized from curcumin and Schiff base ligand and the resulting complexes are characterized by various techniques. Zinc-based complexes are tetrahedral while other metals were square planar. These complexes were examined in antimicrobial studies [50]. Schiff base metal complexes have been prepared by using N-phenyl-o-phenylenediamine and 2-hydroxy-1-napthaldehyde in the presence of Zn(II), Cu(II) and VO(IV). The complexes, characterized using UV–visible, H-NMR and FT-IR, have antibacterial activities [51].

Coordination complexes have been formed by reaction of ligand with VCl_3, $MnCl_2{\cdot}3H_2O$, $NiCl_2{\cdot}6H_2O$ and $ZnCl_2$. The bidentate nature of the ligand gave octahedral geometries. This study has wide application in antibacterial, antitumor and antifungal

activities [52]. Schiff base metal complexes were also prepared from *o*-phenylenediamine, 2-furancarboxaldehyde, 2-aminothiophenol and 2-thiophenecarboxaldehyde and characterized by magnetic moment, ^{1}H NMR, thermal analysis and IR. These complexes were screened for antibacterial and antifungal activities [17].

4.9. Platinum-based Schiff base complexes

Four platinum Schiff base complexes derived from *o*- and *p*-phenylenediamine with salicylaldehyde and 2-furaldehyde were reported to have best antibacterial activity, more effective antimicrobials than ligand [53]. A series of platinum(II) Schiff base complexes were potent anticancer agents and characterized by molar conductivity, IR, EA and ^{1}H NMR. These complexes were tested for DNA interaction with sperm DNA of salmon and their *in-vitro* anticancer activities have been studied [54].

4.10. Iron Schiff base complexes

These complexes were prepared using condensation of sodium 2-hydroxybenzaldehyde-5-sulfonate and amino acids and characterized by conductance measurements and IR spectral analyses. The complexes were screened for antibacterial activity against *Micrococcus bacteria* and *Bacillus cereus* [55]. Metal-based Schiff base complexes have been derived from amino acids and *o*-phthalaldehyde with Co(II), Mn(II), Ni(II) and Cu(II). The Ni(II) and Cu(II) complexes revealed inhibition towards all microorganisms while Mn(II) and Co(II) showed less inhibition and VO(II) complexes reflected no activity against microorganisms [56]. The Fe(III), Mn(III) and Cr(III) complexes of a Schiff base, synthesized from chromene-2,3-dione and 1,4-dicarbonyl-phenyl-dihydrazide, were screened for antimicrobial as well as antifungal activity (Figure 6) [57].

The Schiff base synthesized from benzaldehyde and 4-aminoantipyrine derivatives was tested for anti-inflammatory activity, showing anti-inflammatory activity that could even be used for the treatment of inflammatory diseases [58]. Schiff base 5-nitroisoquinoline showed *in-vitro* activity as an effective anti-malarial agent [59]. This Schiff base inhibited growth of *P. falciparum* to 50%.

4.11. Copper-based Schiff base complexes

Mono-based *i*-propylenetriamine with 2-thiophene-carboxaldehyde copper complexes were tested for antioxidant and anti-inflammatory activity. The compounds hindered carrageenan-based paw rat oedema and other scavenging activity [60]. The Schiff base 3-(4-(benzylideneamino)phenylimino) 4-fluoroindolin-2-one derivatives, synthesized and characterized by ^{1}H NMR and IR technique, were used for analgesic, ulcerogenic and anti-inflammatory activities [61]. A series of Schiff base derivatives of 4-aminophenazone with a variety of aldehydes were synthesized and characterized by ^{13}C-NMR, ^{1}H-NMR and mass spectroscopy. The synthesized compounds were screened for analgesic, antipyretic and anti-inflammatory activities. Carrageenan and histamine induced paw oedema methods have been employed to determine anti-inflammatory activity in mice [62].

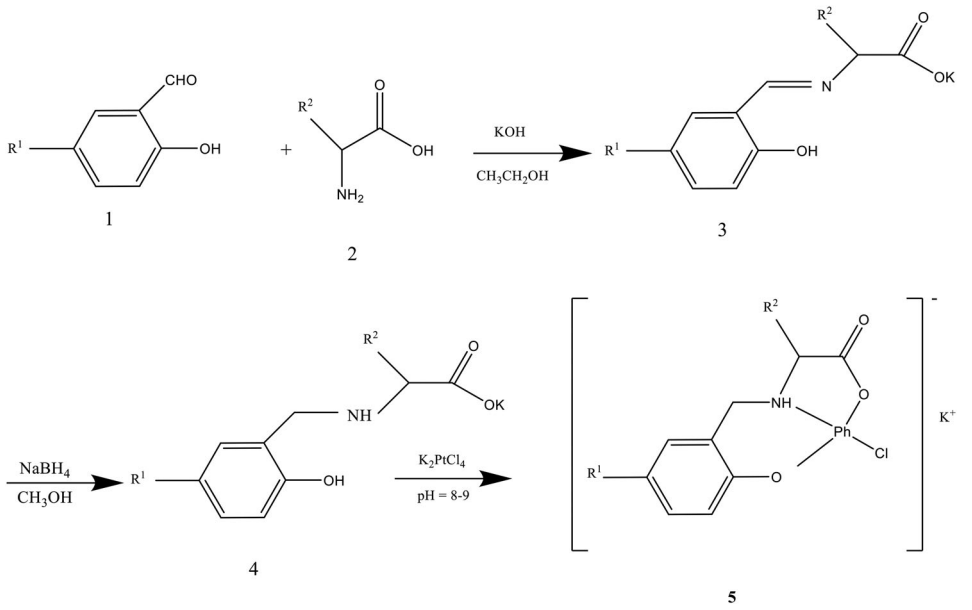


Figure 6. Water-soluble Schiff base complexes reduced amino acid with platinum [2].

A Schiff base has been derived from condensation of 4-fluoroaniline with 5-chloro-salicylaldehyde and a series of Schiff base complexes have been synthesized with Co(II), Cu(II), Zn(II) and Mn(II) with 4-chloro-2-{(*E*)-[(4-fluorophenyl)imino]methyl}phenol in methanol exhibiting great anti-bacterial activity [63]. Copper-based SB complexes were synthesized by condensation of copper complexes with quinoline SB ligands. The synthesized complexes were used to treat human cancers [64]. SB complexes of zinc and copper have been derived by reaction of amine with trimethylsilyl-propyl-*p*-aminobenzoate in the presence of *o*-vanillin and salicylaldehyde. The metal complexes have fluorescent green color with biological properties [65]. Singh *et al.* synthesized Schiff base complexes from 2-nitrobenzaldehyde with amino acids and Ni(II), Cu(II) and Co(II). The prepared ligands and its complexes exhibited great anti-bacterial potential [66].

4.12. Vanadium-based Schiff base complexes

Oxovanadium SB complexes were prepared using $VOSO_4$ under refluxing conditions and electrochemical properties of the compounds where investigated [65], revealing irreversible behavior and one-electron transfer. The VO(II)-based metal complexes were synthesized by mixing methanolic solution of Schiff base and $VOSO_4{\cdot}nH_2O$ in equal proportion with reflux and recrystallized with ethanol [67]. The appearance, yield and geometry of some SB metal complexes are given in Table S1.

4.13. Copper complexes of coumarin-based ligands

The Schiff bases derived from coumarin have been studied using pH-potentiometric and UV-Vis spectroscopy techniques [68]. Coordination of the ligands is *via* nitrogen in

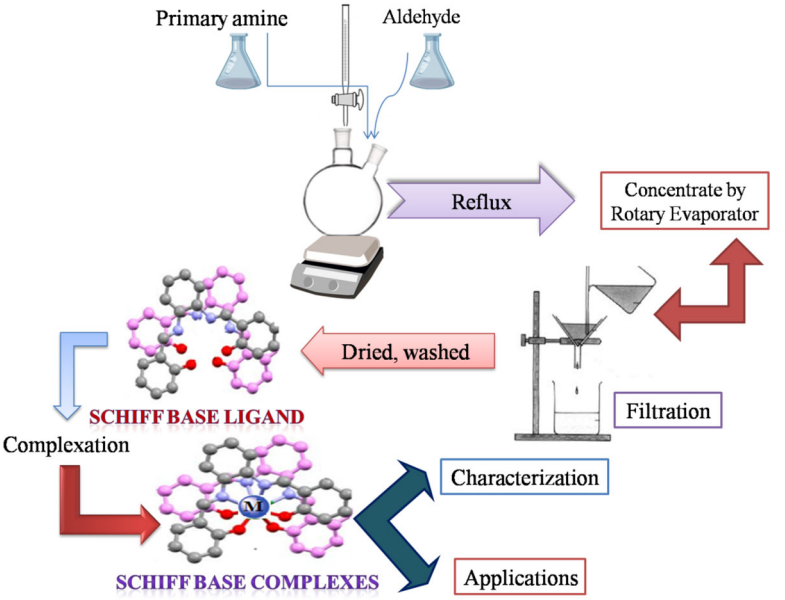


Figure 7. Schematic representation of steps involving in synthesis of Schiff base ligands and metal complexation.

the imine as well as deprotonated phenol. Complexes with copper have good chemotherapeutic potential against colon cancer and breast cancer. Joseyphus *et al.* synthesized Schiff base complexes by reaction of glycylglycine and indole-3-carboxaldehyde in the presence of Cu(II), Co(II) and Ni(II). The Ni(II) and Co(II) complexes have tetrahedral geometry while Cu(II) has square planar geometry. The entire series was screened for anti-microbial activity [65]. Copper, zinc and cobalt complexes have been prepared by reaction of salicylaldehyde and D,L-selenomethionine. The SB is a tridentate ligand towards metal ions. Anti-fungal and anti-bacterial activity of the metal complexes were reported [69]. A general scheme showing different stages of Schiff base preparation and formation of Schiff base metal complexes is sketched in Figure 7.

5. Schiff base surfactants

The surfactants are surface-active materials applied in pharmacology to increase drug efficiency. The application of surfactants in SB has been studied by several groups to overcome challenges. Considering the importance of coordination complexes, the surfactant addition in such materials has also been investigated. Synthesis of a series of surfactant incorporated Cu(II) SB complexes has been carried out for applications including binding to DNA and cytotoxic activity against breast cancer [70]. Complexes bind through the minor groove mode in the presence of a surfactant chain whose length exhibited a role in the binding. The docking study revealed interaction of the metal complexes with DNA *via* alkyl part of the SB. The cytotoxic properties of the complexes against breast cancer exhibited reasonable outcomes. The surfactants applied to materials are highly surface sensitive agents and surface properties are important to know effectiveness of the surfactants. In a study of chemical properties

of a series of cationic SB, surface properties depend strongly on hydrophobic chain length of the surfactant [71]. Analysis of thermodynamic properties revealed that the prepared surfactants adsorbed at the air-water interface when compared to application in bulk solution. The synthesized surfactants are highly efficient to avoid corrosion and acted as biocides for preventing the bacterial growth. The impact of surfactants on SB against corrosion was investigated on steel *via* different techniques [72]. The polarization study of the prepared materials revealed mixed cathodic-anodic nature of the surfactants whereas electrochemical impedance spectroscopic measurements indicated sticking of the molecules of the surfactants on the surface. In a comprehensive investigation by Singh *et al.* the anticorrosive, lubricity, anti-wear and antifriction activities of cationic geminal surfactants 14-MTR-14 and 14-PTR-14 on triazine SB have been reported [73]. The surfactants have been synthesized in two step processes and characterized *via* thermogravimetry and other spectroscopies. The biological activity of SB surfactants has been investigated to explore the effects on drug efficiency for applications in pharmacology. Different cationic SB surfactants, 5-CMS, 4-IMHDAC, 6-IMHDAC and 8-IMHDAC, have been tested for surface as well as biological activities [74]. The increase in chain length of the alkyl enhanced the surface activity and samples exhibited an increased rate of adsorption at the organic-polar phase. The surfactants exhibited good oil recovery as well as antimicrobial activity against bacteria and fungi.

6. Applications in inflammatory diseases

6.1. Inflammation

Inflammation is an immune system's response against illness and injuries. Two types of inflammations are generally known, acute and chronic inflammation. Acute inflammation involves infections like acute typhoid and acute appendicitis and tissue injuries but chronic inflammation deals with a variety of diseases, including cardiovascular diseases and diabetes type 2. Generally, chronic inflammation is not caused by infection and injury but it is associated with malfunction of tissues [75]. The inflammation appearing in different forms helps in diagnosis and hence dealing with causes of the original infection. The cure of infection to address the inflammation is important as the unsettled infection may lead to loss of human organs. Hence, prior to reaching the acute phase of the disease, the infection should be resolved for which case understanding mechanism of inflammation and pharmacological strategies are needed. These techniques are suitable for a number of pre-clinical cases to cure inflammations, which indicates that pharmacological resolutions may act as useful anti-inflammatory treatment [76].

6.2. Non-steroidal anti-inflammatory drugs (NSAIDs)

Most anti-inflammatory drugs are extracted from plant sources to get relief from pain and fever. Non-steroidal anti-inflammatory drugs (NSAIDs) are used as anti-inflammatory drugs. NSAIDs are generally composed of organic acids and later non-acidic compounds. Some anti-inflammatory drugs show less gastrointestinal side effects as

compared to predecessors like aspirin and indomethacin [77]. The main function of NSAIDs is to block the COX enzyme and suppress the activity of prostaglandin. Two types of COX enzymes are known, COX-1 provides protection in gastrointestinal tract while COX-2 performs inflammatory signal activity [78].

6.3. Carrageenan activated oedema

Carrageenan activated oedema has been utilized as an experimental animal representative for acute inflammation and it is attributed to be a biphasic. The initial phase (1-2 h) of the carrageenan model was moderated through histamine, serotonin as well as enhanced fabrication of the prostaglandins within the surroundings of blemish tissues. The later phase was assisted through prostaglandin liberated as well as mediated by leukotrienes, bradykinin, prostaglandings and polymorphonuclear cells generated by tissue macrophages. Compound inhibition to paw oedema is activated through the carrengeenan in the second phase. These findings recommended inhibition of the cyclooxygenase fabrication *via* compound and this impact is the same as that generated through non-steroidal anti-inflammatory drugs like indomenthacin, with a mechanism of action inhibition of the cyclooxygenase enzymes. Shukla *et al.* studied the anti-inflammatory activity of VO(II) complexes by using carrageenan induced paw oedema method in rats (albino). Among all complexes, $[VO(SCA)_2]$ showed the most promising anti-inflammatory activity [78].

6.4. Anti-inflammatory assay

Shukla *et al.* utilized albino rats of nearly the same age and divided them into two categories of control and test groups and kept them in polypropylene cages [78]. They fed them with water and general chow diet with fasting for 12 h before each test. The controlled group animals received 1% acacia gum while the test group got different concentrations and were observed for 48 h. The rats were aligned into seven different groups. Group I was the controlled group while in group II rats were given standard drug diclofenac sodium orally. Groups III-VII were orally regulated with VO(II) complexes. The paw volume was measured by plethysmographic method at 5 h after the injection of carrageenan. A drug was given 1 h before carrageenan injection.

Generally, inflammation is defensive response against cell injuries in animals. The VO(II) complexes were effective against inflammation and results were compared with diclofenac sodium as a standard drug (NSAID). The NSAID shows regular trend from 0.5-5 h and its efficiency ranges from 75-89%. The test complexes have reflected maximum inhibition at 1 h and reduced to minimum at 5 h. The vanadium-based complexes showed very good anti-inflammatory activity out of which $[VO(SCA)_2]$ and $[VO(AAMB)_2]$ have shown maximum inhibition against inflammation. The best anti-inflammatory activity was by $[VO(SCA)_2]$ among all complexes [78].

Jayashree *et al.* studied another carrageenan induced paw pain and oedema through inflammation of paw volume in wistar bred rats placed in polypropylene cages under controlled temperature and humidity conditions [79]. Rats are divided into seven groups with six members in each group. Group 1 contained CMC as a

vehicle while group II is the control group with aspirin. Group III-VII animals included rats containing test compounds and introduced the carrageenan to all animals. The plethysmograph method was used at intervals of 30 min. The increased percentage in paw volume at various intervals was compared with control and respective standards [79].

Carrageenan induced pain and oedema are commonly used for acute inflammation and is a strong inflammatory mediator which activates the inflammation pathway of COX and LOX. The oxygen derived radicals are released during inflammation. The tested compounds have shown DPPH *in-vitro* scavenging activity. The anti-inflammatory activity of aspirin and tested compounds were similar as shown in Table 2 [79]. Another carageenan induced inflammation has been introduced in albino mice of approximately same weight placed in iron cages [80]. The albino mice have been classified into five groups with six animals in each. Group I contained diclofenac sodium while group II is the control group as shown in Table 2. Carrageenan has been introduced in all animals and paw volume was calculated at 30 min intervals using a screw gauge [80, 81]. The % inhibition of respective inflammation has been measured using % inhibition $= (1\text{-}D_t/D_o) \times 100$, where D_t is average inflammation of introduced sample and D_o is considered as average inflammation for the control group.

The micronucleus study of NO can be estimated by either *in-vivo* or *in-vitro* method [84] (Figure 8).

The *in-vivo* method includes exudation and neutrophil migration and paw oedema assay. The exudation model suggested decrease in extravasation by 24-25%. The neutrophil migration revealed decrease in amount of neutrophil of nearly 60%. Lastly, paw oedema model suggested reduction in paw volume at time points. The results showed that production of NO decreased in both *in-vivo* and *in-vitro* studies. These conclusions are strong evidence that nitro Schiff base proved to be a powerful candidate for the cure of inflammatory related diseases.

Sondhi *et al.* studied the same concept of carrageenan induced acute inflammation in albino rats as described by Winter *et al.* [85]. The Schiff base 4,4-bis[1-{(2-aminophenylimino)methyl]naphthalen-2-ol has great anti-inflammatory activity because of the bis nature of compound in comparison to other derivatives [22]. Stolarczyk *et al.* studied the inflammation caused by E. faecalis pathogen and the effect of coordination compounds in comparison to amine [86]. The –C = N– bond in the Schiff base prohibited growth of cancer cell and showed best anti-cancer and anti-bacterial activities as compared to amines.

Cyclooxygenase enzyme is a therapeutic molecule that has been used for synthesis of drugs screened for anti-inflammatory activity. The target compound has been studied by using prepared compounds and indomethacin, a commonly used anti-inflammatory drug. The anti-inflammatory activity of coordination compounds indicated significant anti-inflammatory activity in comparison to that of indomethacin as shown in Table 2 [82]. In the past, diclofenac sodium as a NSAID has been used as an anti-inflammatory drug but because of the presence of COOH group GI toxicity has been associated with it. The Schiff base 1,3,4-oxadiazole has been synthesized from diclofenac acid and characterized by FTIR, TLC and ^{1}H NMR. The compounds exhibited

Table 2. Anti-inflammatory effect of various compounds on carrageenan induced oedema of albino mice and rats.

Compounds/treatment	% of Inhibition				Reference
	30 min	60 min	120 min	180 min	
5% CMC	13.0 ± 0.3	15.3 ± 0.5	16.5 ± 0.4	18.5 ± 0.5	[79]
Aspirin	10.6 ± 0.3	11.3 ± 0.1	12.1 ± 0.1	12.8 ± 0.2	
SA-3	10.8 ± 0.3	10.4 ± 0.2	13.2 ± 0.6	14.7 ± 0.7	
BSJ-3	9.3 ± 0.1	11.2 ± 0.2	12.7 ± 0.3	14.3 ± 0.3	
BSJ-4	9.6 ± 0.4	9.2 ± 0.4	12.0 ± 0.1	13.2 ± 0.3	
BSJA-1	11.3 ± 0.3	11.1 ± 0.7	15.3 ± 0.7	16.2 ± 0.7	
BSJA-4	12.7 ± 0.3	12.9 ± 0.2	13.5 ± 0.3	15.5 ± 0.1	
Control (Saline)	2.8 ± 0.2	6.4 ± 0.6	7.3 ± 0.7	8.0 ± 0.8	[80, 81]
Diclofenac sodium	0.6 ± 0.2	1.2 ± 0.4	1.3 ± 0.4	0.9 ± 0.4	
VO(AAIT)	1.3 ± 0.3	3.1 ± 0.4	3.0 ± 0.5	3.6 ± 0.4	
VO(ANIT)	1.2 ± 0.4	2.5 ± 0.5	4.4 ± 0.6	2.5 ± 0.4	
$VO(SCA)_2$	0.2 ± 0.1	0.5 ± 0.3	1.9 ± 0.3	2.7 ± 0.4	
Control (1,3,4-oxadiazole)	0 ± 1.	0 ± 1.	0 ± 1.	–	[82]
Iodomethacine	38.8 ± 0.6	56.6 ± 0.7	68 ± 1	–	
5-(2-(2-bromobenzylideneamino)phenyl)-1,3,4-oxadiazole2-thione (4a)	8.2 ± 0.8	26.8 ± 0.9	34.5 ± 0.7	–	
5-(2-(3-bromobenzylideneamino)phenyl)-1,3,4-oxadiazole2-thione (4b)	20 ± 1	38 ± 1	47.1 ± 0.9	–	
5-(2-(3-bromobenzylideneamino)phenyl)-1,3,4-oxadiazole2-thione (4b)	24 ± 1	42 ± 1	51.7 ± 0.8	–	
5-(2-(4-methoxybenzylideneamino)phenyl)-1,3,4-oxadiazole-2-thione (4d)	16 ± 1	32 ± 1	40.2 ± 0.8	–	
5-(2-(4-fluorobenzylideneamino)phenyl)-1,3,4-oxadiazole2-thione (4e)	18.4 ± 0.9	35.3 ± 0.9	43 ± 1	–	
5-(2-(2-chlorobenzylideneamino)phenyl)-1,3,4-oxadiazole2-thione (4f)	12 ± 1	29 ± 1	39 ± 1	–	
5-(2-(3-chlorobenzylideneamino)phenyl)-1,3,4-oxadiazole2-thione (4 g)	14.2 ± 0.8	30 ± 1	41 ± 1	–	
5-(2-(4-chlorobenzylideneamino)phenyl)-1,3,4-oxadiazole2-thione (4h)	16 ± 1	33 ± 1	42.5 ± 0.9	–	
5-(2-(4-hydroxybenzylideneamino)phenyl)-1,3,4-oxadiazole-2-thione (4i)	28.6 ± 0.9	46 ± 1	54.0 ± 0.6	–	
5-(2-(2-nitrobenzylideneamino)phenyl)-1,3,4-oxadiazole-2-thione (4j)	10 ± 1	28 ± 1	37.9 ± 0.8	–	
Control	–	–	1.9 ± 0.1	2.01 ± 0.09	[83]
Iodomethacine	–	–	0.5 ± 0.1	0.4 ± 0.1	
2-(2-(4-Chlorophenyl)-5-hydroxy-1H-imidazol-1-yl)benzoic acid (3c)	_	_	0.5 ± 0.1	0.4 ± 0.1	
1-(4-Chlorophenyl)-7,8-dimethoxy-4-(methylamino)imidazo[1,5-a]quinazolin-5(4H)-one (6)	_	_	1.6 ± 0.2	1.1 ± 0.2	
1-(4-Fluorophenyl)-4-(3-phenylallylidene)amino) imidazo[1,5-a]quinazolin-5(4H)-one (8b)	_	_	1.0 ± 0.1	0.9 ± 0.1	
4-Chloro-N-(1-(4-chlorophenyl)-5-oxoimidazo[1,5-a]quinazolin-4(5H)-ylcarbamothioyl)benzamide (11i)	_	_	0.7 ± 0.2	0.7 ± 0.1	
2-(1-(4-Fluorophenyl)-5-oxoimidazo[1,5-a]quinazolin-4(5H)-ylamino)-2-oxoethyl 2-(4-isobutylphenyl)propanoate (14c)	_	_	0.41 ± 0.09	0.5 ± 0.1	

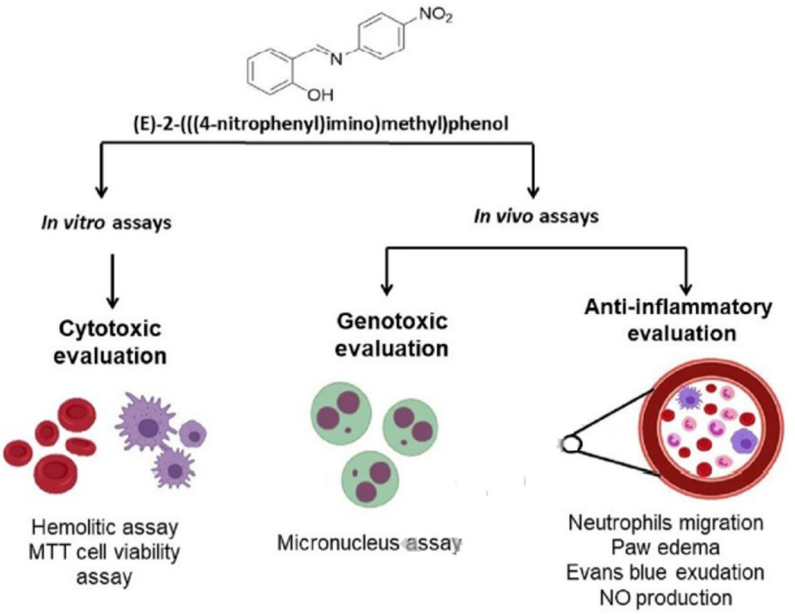


Figure 8. The micronucleus study of NO by either *in-vivo* or *in-vitro* method. The usage of nitro Schiff base for cure of inflammatory related diseases. Reprinted with permission from reference [84] Copyright 2020, open access, Elsevier.

significant anti-inflammatory activity in carrageenan induced rat oedema as compared to Diclofenac sodium [87].

Amateisosteres SBs have been carried out for exploring anti-inflammatory and analgesic activity. The anti-inflammatory activity has been evaluated by carrageenan oedema. The resulting compounds exhibited excellent analgesic and anti-inflammatory activities as shown in Table 2 [83, 88]. The series of quinazolinone-based Schiff bases has been screened for anti-inflammatory and antioxidant activities. The antioxidant activity of coordination compounds has been compared with gallic acid, ascorbic acid and butylated hydroxytoluene. The synthesized compounds have excellent anti-inflammatory activities [24]. The utilization of SBs as anti-inflammatory agents has been investigated by several groups. Different aromatic aldehydes have been used to prepare SB ligands [83, 87]. The prepared materials have been characterized for analgesic activity and anti-inflammatory property against albino mice [89]. The analysis revealed good activity of the SBs against *Staphylococcus aureus* and *E. coli* bacteria.

To study antioxidant activity of coumarin structured SB, *in-vitro* radical activity screenings have been conducted [90, 91]. The free radical scavenging properties of some compounds improved when compared with a standard antioxidant, butylated hydroxytoluene. The free radical scavenging activity of a compound is improved when compared with antioxidant ascorbic acid [92]. The biological applications of several SB ligands have been evaluated to investigate antioxidant activity using different spectroscopic techniques [93]. Compounds with hydroxyl groups at appropriate positions exhibited good radical scavenging and antioxidant activities [94, 95]. The complexing ability of oxime SB to lanthanide ions for applications in single molecular magnets has been reported [96]; to enable the SB metal complexes for magnetic properties and

relevant applications [97], the magnetic properties of five-coordinate neutral chloro-iron complexes revealed high-spin atomic configuration with five unpaired electrons. Similarly, Mn-based Salen type complexes exhibit magneto-anisotropic properties [15].

7. Recommendations

Research activities on drugs, nanomaterials and new compounds for different applications are in active mode [98–101]. NSAIDs are capable to inhibit cyclooxygenase whereas SAIDs avoid arachidonic acid to reduce formation of prostanoids and leukotrienes [102]. Anti-inflammatory drugs react with oxidants causing considerable attention to the role of oxidant scavenging in drug action [103]. Though much research has been done to search NSAIDs, safe and secure drugs with required efficiency are still needed, especially when novel inflammations are reported. For instance, strategies are in progress to resolve COVID-19 related life threatening inflammations [104]. Complexation of Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II) and Cd(II) with SB ligands forming coordination complexes have been reported to tackle COVID-19 [105–117]. A complex involving Mn appeared to offer less binding energy when compared with bare SB, which points to improved anti-viral property of the material. Similarly, SB upon complexation with Co(II), Ni(II), and Cu(II) have been clinically tested to fight against COVID-19 and prostate cancer [110, 118–120]. In a recent study, new SB compounds, EMHT, have been studied *via* different techniques including first-principles molecular dynamics to fight against inflammations caused by corona virus [121]. Protein binding has been theoretically predicted when tested for 6-NUR protein [122]. The anti-fungal, anti-tumor, anti-bacterial, and anti-virus properties of Schiff bases are well documented but less is known of their anti-inflammatory activity. This review is dedicated to the contributions made on preparation of NSAIDs with the recommendation that more efforts are required by the community to explore further potential of Schiff base metal complexes to cure inflammations in the human body.

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Disclosure statement

The authors declare no conflicts of interest.

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