Biological Study and synthesis of Schiff bases metal complex using ionic liquid/green method

VISHVAS G. CHOUDHARI [a], ANIL S. KIRDANT [b], SHARAD K. PASALE *[c]

[a] Dept.of Chemistry Karamveer Mamasaheb Jagadale Mahavidyalaya,Washi, District-Osmanabad Email- choudhari.vishvas@gmail.com

[b] Dept. of Chemistry, Baburaoji Adaskar Mahavidyalaya Kaij Dist Beed Email-dr.askirdant@gmail.com

c Dept. of Chemistry, Thakur College of Science and Commerce, Kandivali (E), Mumbai

sharadpasale@gmail.com

Abstract

As a green chemistry approach for synthesizing organic molecules, the use of microwave to expose reactants with or without solvents is explored here. Analytical, inorganic, and organic chemists all employ Schiff bases (SBs) in their work. The need for SB synthesis is further emphasized by a broad variety of pharmacological and biological functions, including analgesic, antiproliferative, antiviral, anti-inflammatory, antibacterial, antipyretic, and antifungal activities. In a variety of processes particularly when there is moisture present, several Schiff base complexes have good catalytic activity. The study of these compounds' coordination behavior has significantly increased because of the impact that specific metals have on their biological properties and its inherent chemical significance as multidentate ligands. The overview of the synthesis of SBs and its metal compounds Schiff bases and its metal complexes using various green methods and ionic liquid techniques is discussed here. Examples of the most promising applicable SBs and its metal compounds from many fields are included in this overview.

Keywords: *Biological activities, Green chemistry, Ionic liquid method, Metal complexes, Schiff bases.*

1 Introduction

A Schiff base is a nitrogen analogue of an aldehyde or ketone wherein the carbonyl group (CO) has been swapped out for an imine or azomethine group structurally [1]. Any primary

amine may react with an aldehyde or a ketone to produce a Schiff base under appropriate circumstances.

Fig. 1: Common concept for establishing SBs [2]

Drug design techniques often use organic reactions involving the condensation of two or more molecules to create new compounds with novel biological properties [3]. Schiff bases are the result of condensation reactions involving primary amines along with artificially produced ketones or aldehydes. Schiff bases play a key role in a variety of industrial and catalytic processes as well as a wide range of biological functions. They may also stabilize metal ions in different oxidation states [4, 5]. The nitrogen lone pair of electrons in azomethine (N = CH) bonding in their structure is what causes stable complexes to form with metal ions [6]. In several crucial biochemical processes, bioinorganic chemistry, supramolecular chemistry, and molecular magnetism, such stable compounds play a significant role [7]. Imine complexes possess a variety of biological characteristics, such as antibacterial, antiviral, antifungal, and anticancer activities [8]. They are widely explored as antimalarial drugs and are used to treat medicine resistance in cancer. They could also be used to immobilize enzymes [9].

Numerous Schiff base ligands and its complexes have been studied for their intriguing and significant characteristics, including their photochromic properties, their capability to reversibly bind oxygen, their ability to complex with some toxic metals, and their catalytic properties in the hydrogenation of olefins. However, other Schiff base complexes have excellent biological action and biological modelling applications [10].

1.1 Green chemistry

A more modern approach to studying organic synthesis as well as drug design methods is known as "green chemistry" [11]. It is that area of chemistry that deals with tools, methods, and apparatuses and offers considerable economic and environmental advantages over traditional synthetic techniques [12]. The present focus on green chemistry has posed several challenges for organic synthesis, from which it is necessary to construct contemporary reaction conditions that entail reducing the usage of organic solvents or harmful compounds [13].

In contrast to conventional approaches, many of the processes used by green chemists use solvent-free reactions, simplify workup procedures, reduce reaction time, improve selectivity, and streamline purification operations [14]. The first synthesis of Schiff bases (imines) was documented by Hugo Schiff in the 19th century. An aldehyde with an azomethine -N=CH- group in place of a C=O group is referred to as a Schiff base. Typically, it is created when primary amines and aldehydes react [15]. RCH=NR1 (R & R1 characterizes alkyl or aryl substituents) is the common chemical expression for Schiff bases [16].

1.2 Ionic liquid method

Ionic liquids (ILs) are "ionic materials" with low melting temperatures (below 100°C), often made up of massive, typically asymmetric organic cations and inorganic or organic anions. When used in place of conventional molecular solvents, ionic liquids (ILs) have a variety of unique physicochemical and solvation features that may be tailored for purposes and often produce fascinating results [17]. Additionally, the majority of ILs have low vapor pressure [18] and great thermal stability [19]. They are known as neoteric solvents or green solvents because of these appealing characteristics. Due to their large electrochemical window, high ionic conductivity [20], and wide temperature range of the liquid state, ILs have received a lot of attention in recent years. Additionally, by altering their cation and anion pairing, ILs' physical characteristics, including density, melting temperature, polarity, Lewis acidity, viscosity, and enthalpy of vaporization, may all be adjusted [21]. The improved reaction kinetics that an IL-based solvent solution often demonstrates allows for the efficient use of both time and energy [22]. These characteristics make ILs an effective substitute for traditional media in chemical processes as well as a new generation of solvents for catalysis, environmentally friendly reaction media, and organic synthesis [23]. Functionalized ionic

liquids (FILs), which include various functional groups in the cationic moiety, have recently attracted the attention of numerous researchers [24]. Both the cationic and anionic moieties of the FILs may be changed as needed for applications such as greater catalytic stability and decreased catalyst leaching, etc. by readily functionalizing the cation in a single chemical step [25].

1.3 Schiff Bases with Antibacterial Activity

Gram-negative, Gram-positive, *E. coli*, *Pseudomonas aeruginosa* as well as *Bacillus cereus*, were inactive against two series of schiff base derivatives containing anthracene/pyrene units, as disclosed by **Gumu et al. (2020)** [26]. Tetracycline (30 μg) and streptomycin (10 μg) discs were used as positive controls in these studies, which were carried out using the disc diffusion technique. Agarose gel electrophoresis, which measures how DNA molecules respond to changes in mass, charge, and shape, was also used to investigate DNA binding activities. Free DNA travels more quickly across the gel because it is smaller than bound DNA because of the chemicals binding to calf thymus DNA (CT-DNA). It should be noted that compounds 5 and 6, respectively, "(E)-2-((anthracen-1-ylimino)methyl)quinolin-8-ol and "(E)-2-((pyren-1-ylimino)methyl)pyridin-3-ol", were observed to be bounded stable to CT-DNA and had antibacterial action against *E. coli* and *Bacillus cereus*.

Three SBs were synthesized, and their antibacterial activity was assessed using the disc diffusion test in a study by **Warad et al. (2020)** [27]. In comparison to gentamicin, the compounds had little action. "2-(piperazin-1-yl)-N-(thiophen-2-ylmethylene)-ethanamine (17)" [28] was the most intriguing molecule. Compared to *P. aeruginosa* (IZD = 16 mm) and gentamicin (IZD = 25 and 24 mm, respectively), the most susceptible isolates to this substance were methicillin-resistant *S. aureus* (MRSA) and Gram-positive *S. aureus*.

Hassan et al. (2019) [29] demonstrated the antibacterial efficacy of "5-(benzylideneamino)-3-(4-methoxyphenylamino)-N-phenyl-1H-pyrazole-4-carboxamides" against MDRB (multidrug-resistant bacteria). Particularly, compound 1 had comparable activity to the reference against the Gram-positive *E. faecalis* (MIC = 7.81 μg/mL), that causes serious infections in humans whereas compounds 2 through 3 were more effective than ciprofloxacin against the *S. epidermidis* (15.62 μg/mL versus MIC = 7.81 μg/mL of ciprofloxacin) [30].

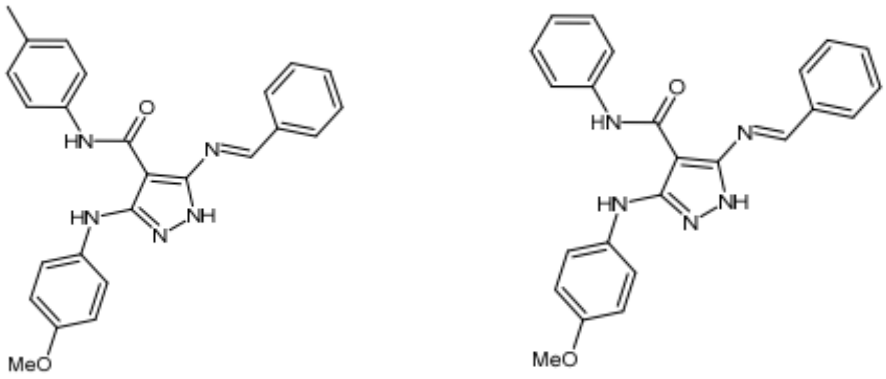


Fig. 2. Compound 1 and 2

1.4 Schiff base with antifungal activity

Worldwide reports of severe fungal coinfections and a variety of COVID-19-related candidemia outbreaks in hospital critical care units have been made as of 2020 [31]. A multispecies panel strains of Candida was used to assess the SBs of sulphonamides first (*Candida albicans* NCPF3179, and NCPF3281 *C. auris* TDG1912, *Candida tropicalis* NCPF8760, *Candida krusei* NCPF3876, *Candida glabrata* NCPF8018, and *Candida parapsilosis* NCPF3209). MIC values for compound 3 against virtually all strains were noteworthy, falling between 4 and 32 μg/mL (compared to fluconazole's 0.5 ≥128 μg/mL). As a result, it was examined against a wider range of MDR (multi-drug resistance) *C. auris* strains (TDG2211, NCPF8977, TDG2512, TDG2506, TDG1102, NCPF8971, and NCPF8984), and its antifungal properties was approved with MICs of 4–16 μg/mL, that are incredibly low when you consider that in four cases, TDG2211, TDG1102, TDG2506, and NC. Only on the expanded panel did compound 4 exhibit the same outcomes as compound 40.

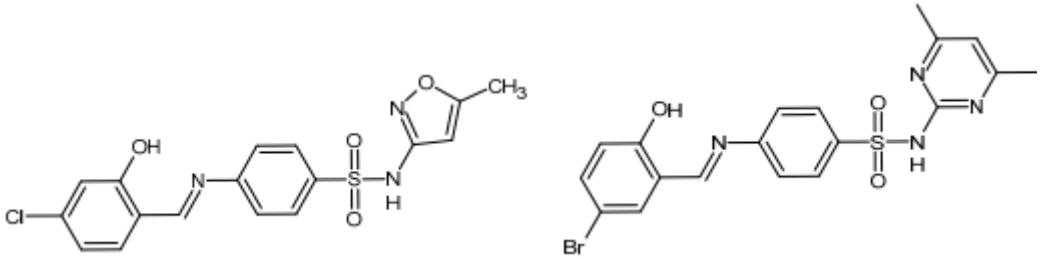


Fig. 3. Compound 3 and 4

To increase the biological activity of inulin, **Chen et al. (2020)** [32] reported a structural alteration of inulin by SBs. According to Guo's technique [33], antifungal investigations conducted on three different types of plant pathogenic fungus (*Phomopsis asparagi, Fusarium oxysporum* f. *sp. cucumerium* Owen, and *Botrytis cinerea*) revealed that synthesized inulin derivatives have a wide antifungal range. The IIs (Inhibitory Index) of compound 5 were 93%, 83%, and 82% against *F. oxysporum f. sp. cucumerium* Owen, *B. cinerea*, and *P. asparagi*, respectively, at 1.6 mg/mL. compound 5 can quickly enter cells owing to its lipophilic properties brought on by the presence of the benzene ring and acetyl groups, which causes apoptosis. Additionally, through interacting with cellular components, the novel inulin compounds altered with Schiff bases demonstrated a superior metal binding property, inhibiting microbial development.

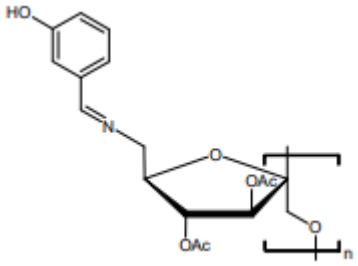


Fig. 4. compound 5

23 cinnamyl SBs were created, and there in vitro antifungal effectiveness was evaluated by **Magalhes et al. (2020)** [34]. Six of them demonstrated antifungal properties against strains of Cryptococcus species in particular as well as *Candida sp., Aspergillus sp.*, and Fonsecaea. Fluconazole, on the other hand, proved ineffective against all Cryptococcus strains, regardless of species. It was found that fluconazole had a MIC more than two times lesser against all strains of *C. neoformans* (1.4 µg/mL and MIC = 1.33 µg/mL in that order), versus fluconazole, 5.2 µg/mL) and that the compounds 6 and 7 did not significantly harm human kidney, lung, or RBCs, all of which had selectivity indices over 10.

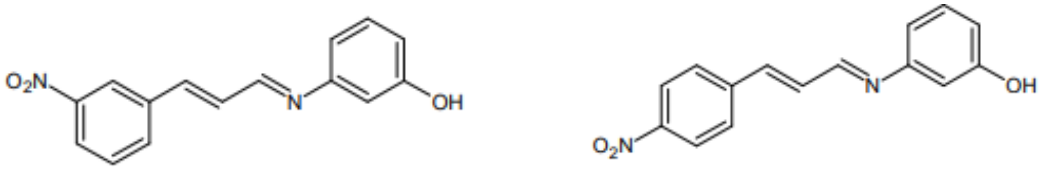
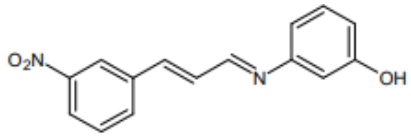
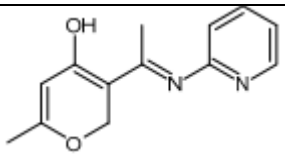
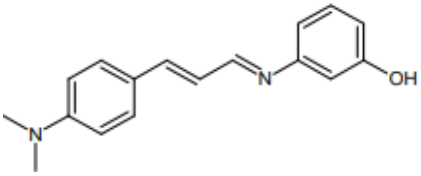
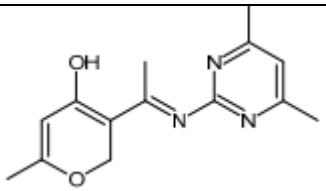
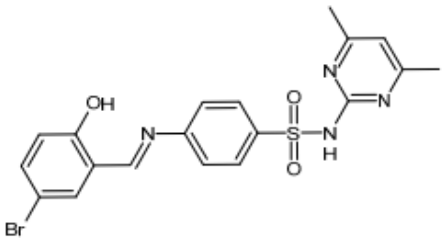
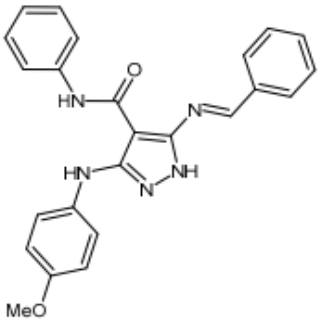
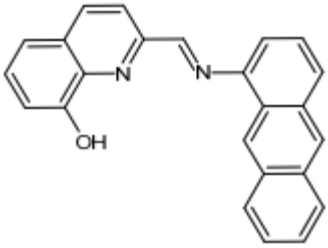
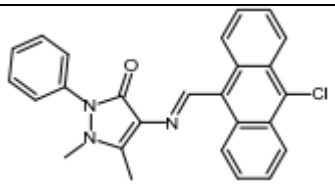
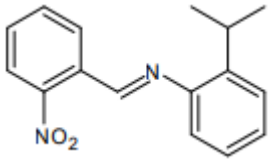


Fig. 5. compound 6 and 7

Table 1. Schiff bases with antimicrobial properties			
Compound	**Structure**	**Antimicrobial properties**	**References**
Antifungal activity			
23 cinnamyl Schiff base (6)		MIC=1.33µg/mL (*C. neoformans*) MIC = 1.33µg/mL (*C. gatii*)	**[34]**
Schiff base of "2-amino-4, 6-dimethylpyrimidine"		IZD (Inhibition zone diameter) = 21 mm (C. albicans)	**[35]**
23 cinnamyl Schiff base (7)		MIC = 3.2 µg/mL (*C. neoformans*), MIC = 8.0 µg/mL (*C. gatii*)	**[34]**
Schiff base of "2-amino-4, 6-dimethylpyrimidine"		IZD = 19 mm (mm (*A. niger*)	**[35]**
"4-(5-bromo-2-hydroxybenzylideneamino)-N-(5-methylisoxazol-3-yl) benzenesulfonamide"		MIC = 16–32 µg/ml (*C. auris* TDG1102, TDG2211), MIC = 16 µg/mL (*C. auris* TDG2512, TDG2506, NCPF8984, NCPF8977), MIC = 8–16 µg/mL (*C. auris* NCPF8971)	**[36]**
Antibacterial activity			

"5-aminopyrazoles, namely 5-(benzylideneamino)-3-(4-methoxyphenylamino)-N-phenyl-1H-pyrazole-4-carboxamides"		MIC= 7.81 µg/mL (*S. epidermidis*)	**[37]**
"(E)-2-((anthracen-1-ylimino)methyl)quinolin-8-ol"		IZD = 13 mm (13 mm (*B. cereus*)	**[29]**
"4-(((10- chloroanthracen-9-yl)methylene)amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3- one"		MIC= 12.5 µg/ml (*A. niger* 9642) MIC=12.5 µg/ml (*S. aureus* 23235)	**[29]**
"(E)-2-isopropyl-N-(2-nitrobenzylidene) aniline"		MIC = 15.625 (*S. thyphymurium*) MIC= 125 µg/Ml (*E. coli*)	**[38]**

1.5 Synthesis of "1-{2-(2-hydroxy-5-chlorobenzylamine) ethyl}-3-methylimidazolium tetrafluoroborate".

Sinha et al. (2020) [39] synthesised "1-2-(2-hydroxy-5-chlorobenzylamine) ethyl-3-methylimidazolium tetrafluoroborate", a Schiff base supported by ionic liquid and characterized by several analytical (molar conductance, element analysis, and magnetic susceptibility measurements) and spectroscopic (UV-Visible, SEM, PXRD, ESI-MS, FT-IR, 1H NMR, and 13C-NMR) techniques. Tetra coordinated as well as hexacoordinated structures were ascribed to the synthesized metal complexes based on this spectral data and spectra. The complexes' molar conductance revealed their (1:2) electrolytic character. The Schiff base ligands and its complexes were evaluated for in vitro antibacterial activity against several naturally accessible gram-positive and gram-negative bacteria to determine their inhibitory potentials. Cu(II) complex created the maximum inhibition zone in

Klebsiella pneumoniae plates whereas *Bacillus cereus* plates produced the least inhibition zone.

1.6 Synthesis of "1-{2-(2-hydroxy-5-nitrobenzylideneamino)ethyl}-3-ethylimidazolium tetrafluoroborate"

Sinha et al. (2019) [40] synthesized new Co(II), Ni(II), and Cu(II) metal complexes from the Schiff base "1-(2-hydroxy-5-nitrobenzylideneamino)ethyl-3-ethylimidazolium tetrafluoroborate", which was supported by an imidazolium ionic liquid. These complexes were then characterized using a variety of analytical and spectroscopic methods, including elemental analysis (CHN analysis), UV Tetra coordinated 1:2 metal-ligand stoichiometry for the metal complexes was proposed based on these spectroscopic and analytical findings. The complexes' molar conductance measurements demonstrated their electrolytic character. To evaluate their potential for inhibition, the produced complexes and the ligand were tested for in vitro antibacterial activities against Gram-positive and Gram-negative bacteria. The complexes were quite successful in fighting off the tested organisms.

1.7 Synthesis of "4-chloro-2-{(E)-[(4-fluorophenyl) imino] methyl}phenol" ($C_{13}H_9ClFNO$)

Ommenya et al. (2020) [41] synthesized the Schiff base ligand, "4-chloro-2-(E)-[(4-fluorophenyl) imino] methylphenol" ($C_{13}H_9ClFNO$), to create a novel series of Cu(II), Mn(II), Co(II), Zn(II), and Ni(II), complexes. The condensation reaction between "5-chlorosalicylaldehyde" and 4-fluoroaniline, took place at room temperature. The Schiff base as well as the metal complexes were characterized by elemental composition, UV-Vis, FT-IR, and NMR spectrum data, molar conductivity measurement, and melting temperatures. According to the results of the elemental analysis, the metal complexes that were created had the general formulas $[M(L)_2(H2O)_2]$, where M = Mn, Co, Ni, Cu, and Zn and L = Schiff base ligand ($C_{13}H_9ClFNO$). The "O" and "N" donor atoms of the Schiff base ligand participated in coordination with the metal (II) ions based on FT-IR, electronic spectra, and NMR data; as a result, a six coordinated octahedral geometry was postulated for all these complexes. The compounds were nonelectrolyte, according to investigations on their molar conductance. Using the disc diffusion technique, the (Schiff base ligand and its metal (II)) complexes were evaluated in vitro for their bactericidal efficacy against Gram-positive (*B. subtilis* and *S. typhi*) and Gram-negative (*E. coli* and *P. aeruginosa*) microorganisms. The

metal (II) compound have more antimicrobial action than the free Schiff base ligand, according to the findings of the antibacterial examination.

Table 2. Some Schiff base metal complexes synthesis by green method/ionic liquid method

Compounds	Methods	Antimicrobial activity	References
"1-{2-[(2-hydroxy-5-bromobenzylidene)amino]ethyl}-3-ethylimidazolium tetrafluoroborate"	Ionic- liquid	Gram-negative and positive bacteria are both susceptible to in vitro antibacterial activities.	[42]
"1-(((1H-1,2,4-triazol-3-yl) imino) methyl) naphthalen-2-ol (TMN)"	microwave irradiation technique (green synthesis)	Compound showed antimicrobial activity against bacterial and fungal strain	[43]
"3-(2-hydroxy-3-ethoxybenzylideneamino)-5-methyl isoxazole and 3-(2-hydroxy-5-nitrobenzylidene amino)-5-methyl isoxazole"	condensation	Antibacterial activity showed against against *Aspergillus niger* and *Rhizoptonia solan.*	[44]
"1,4-dicarbonyl-phenyl-dihydrazide and chromene-2,3- dione"	Green method	Show slightly lesser properties against *Rizoctonia sp.,* antifungal activity against *Aspergillus sp.,*	[45]
"N,N-Bis-(2-hydroxyl-5-methoxybenzaldehyde)-mphenylenediamine"	microwave assisted synthesis approach (green method)	Shown antibacterial activity against *Bacillus thuringiensis, Bacillus subtilis, Klebsiella pneumoniae* and *Escherichia coli.*	[46]
N-salicylidene-2-aminophenolate dioxidomolybdenum complexes	Ionic- liquid	Catalytic activity	[47]

1.8 Ni-Based Transition Metal Complexes with Schiff Bases

1.9.1 Schiff - Base Compounds' and its Antimicrobial Activity

Two novel metal complexes with the general formula M(Hαft)2 were created by **Hossain et al. [48]** using an asymmetric Schiff base ligand (HL = Hαft)2 generated from amoxicillin and α-formylthiophene. The antimicrobial response study points to the Hαf (Ligand) and M(Hαft)2 complexes as having promised antibacterial properties against 4 experimental harmful bacteria, namely *P. aeruginosa*, *P. vulgaris, E. coli,* and *S. aureus*, despite being less effective than the amikacin standard medication.

Mishra et al. (2012) [49] produced Schiff base metal complexes of Ni(II), Co(II), and Cu(II) generated from "4-chlorobenzylidene-2-aminothiazole" (CAT) and "2-nitrobenzylidene-2-aminothiazole" (NAT). The Gram-positive bacteria *S. aureus* as well as Gram-negative bacteria *E. coli* as well as the fungus *Aspergillus niger* and *Candida albicans* were tested using the metal complexes of Schiff base. According to the antibacterial results, all pathogenic species were more effectively inhibited by metal complexes than by their Schiff base ligand parents (Figure 6). Additionally, as the concentration rises, the chemicals more strongly suppress bacterial and fungal development.

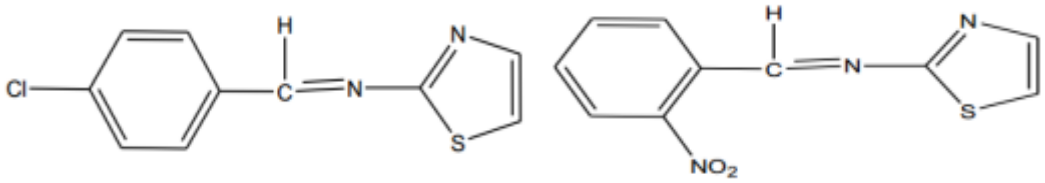


Figure 6. Structure of Schiff base ligand. (a) "4-chlorobenzylidene-2-aminothiazole" (CAT) (b) "2-nitrobenzylidene-2-aminothiazole" (NAT)

"2-Amino-4(4'-methylphenyl)-thiazole" and the Schiff base "4-Acyl-1-phenyl-3-methyl-2-pyrazolin-5-ones" were condensed. These Schiff bases combine to create complexes of form $ML_2.2H_2O$ (M = Ni, Fe, Mn, Cu and Co) (Figure 7). The compounds were examined in vitro using the Agar cup assay method for its antimicrobial properties against *E. coli*, a gram-negative bacterium that causes diarrhea, *Bacillus subtillis*, a gram-positive rod that causes general contamination, and *S. aureus*, a gram-positive spore-forming bacteria that causes wound infections [50].

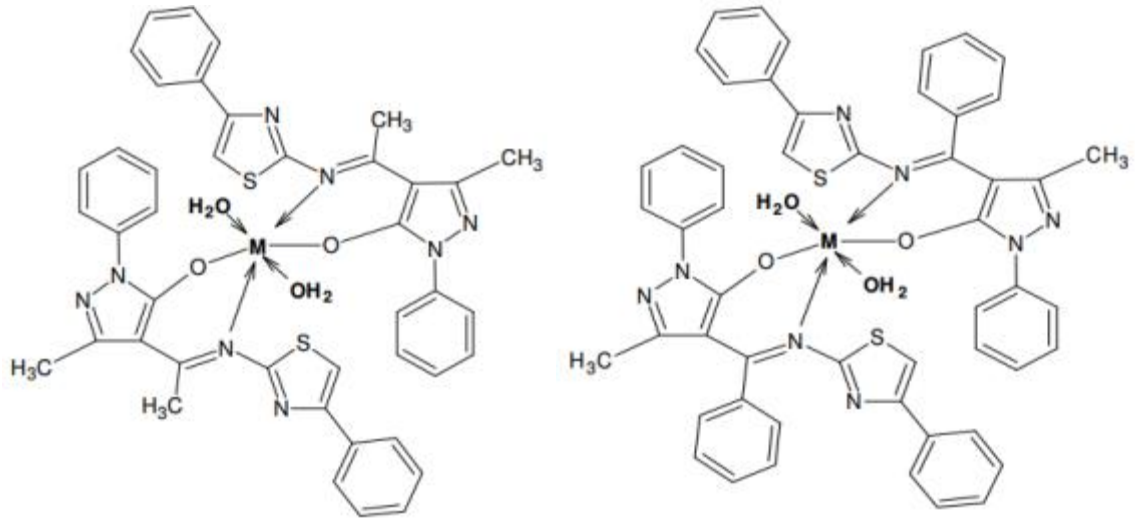


Figure 7. Schiff base metal complexes' structure.

Anacona et al. (2014) [51] produced transition co-ordination compounds containing a Schiff base (HL) generated from the combination of the antibiotic cephalexin with sulphathiazole. The Schiff base (HL) was created when sulphathiazole and cephalexin antibiotic condensed (Figure 8). *E. coli*, a Gram-negative bacterium, and *S. aureus*, a Gram-positive bacterium, were examined for Schiff base ligand as well as metal complex antibacterial properties using a revised Mueller–Hinton agar media as well as Kirby–Bauer disc diffusion method in normal conditions.

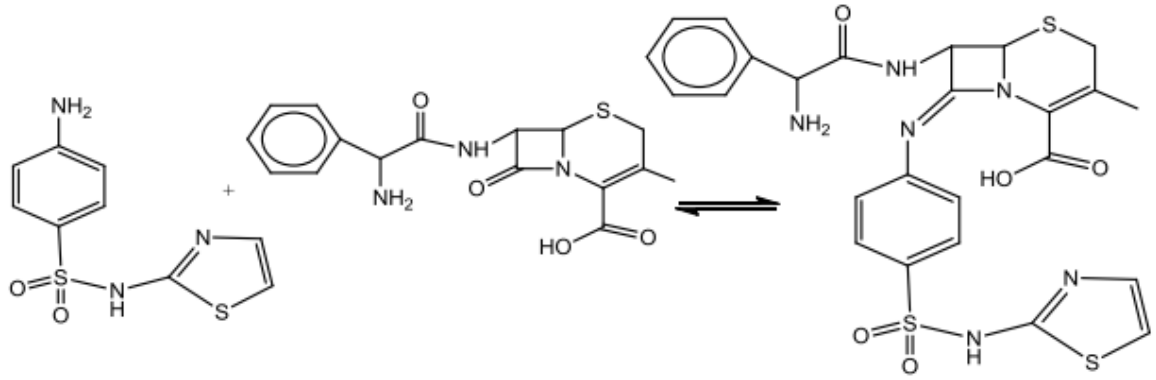


Figure 8. The process of making a Schiff base ligand

Conclusion

Due to their capacity to form metal complexes as well as their pharmacological characteristics, Schiff bases are regarded as a particularly significant family of organic chemicals. The past several years has seen a surge in interest in transition metal complexes containing Schiff bases, partly due to their many biological uses and potential for use in the development of novel medicines. However, more research into the biological effects of these already-created transition metal complexes as well as the creation of novel complexes with additional features are still required. Understanding the characteristics of both metals and ligands may help in the synthesis of highly active compounds since the activity is often improved via complexation. To further understand how these compounds interact with metals, researchers are looking at how they interact with metals and how they interact with other ligands.

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