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REVIEW

Recent Advances in Anti-Urease Activity of Schiff Bases and their Metal Complexes

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The urease enzyme, found in plants, fungi and bacteria, plays a crucial role in catalyzing the hydrolysis of urea, a process integral to microbial metabolism. Its ureolytic activities have garnered significant attention for their impact on agriculture and the health of living organisms. Notably, urease activity in the human stomach, urinary tract and animal cells can lead to pathogenic outcomes. Schiff bases, characterized by their carbonyl-type imine or azomethine linkage, are recognized for their diverse biological effects, including anti-urease activity. Additionally, the metal complexes derived from the Schiff bases demonstrate controlled urease inhibition activity, influenced by factors such as the type of metal, its oxidation state and the coordination environment. This inhibition occurs through the interaction of the Schiff base ligand with the nickel containing active site of urease or the protein sphere surrounding the metal, disrupting the ureolytic mechanism. In this review, the utilization of Schiff bases and their metal complexes in urease inhibition is highlighted as explored by various research groups.

Keywords: Schiff bases, Metal complexes, Anti-urease activity.

INTRODUCTION

A nickel containing metalloenzyme, urease (Fig. 1), also known as urea amido hydrolase [EC 3.5.1.5], belongs to the family of amidohydrolases and phosphotriesterases and is prevalent in soil. Urease was initially crystallized from a plant source, *Canavalia ensiformis*, marking the first crystallization of a metalloenzyme from plants. Furthermore, this enzyme is found in various bacteria [1,2], fungi [3], algae [4] and plants [5]. Its role is pivotal in enabling the utilization of urea as a nitrogen source for plants [6]. Urease catalyzes the hydrolysis of urea, initially producing ammonia and carbamate, followed by the decomposition of carbamate into another molecule of ammonia and carbon dioxide [7]. In agricultural contexts, the hydrolysis of urea by urease leads to soil nitrogen fertilization reduction [8], which can result in soil and root damage, as well as ammonia volatilization [9]. Consequently, urease inhibitors are employed to manage urea hydrolysis in soil [10,11]. Besides having advantages of increasing urea metabolism into soil [12], urease have unfavourable side effects in organisms, such as inhibition of DNA synthesis [13], depressed bone marrow biosynthesis [14] and a heavy dose can result into teratogenesis [15,16]. Urease inhibitors decrease environmental pollution [17] and during the germination process, urease enhances nitrogen metabolism pathways of plants [18]. The importance of urease as urea hydrolyzing enzyme can be realized from the evidence that uncatalyzed hydrolysis of urea takes place very slowly as it has a half-life of 3.6 years while the urease catalysis does this process in microseconds [19,20] (**Scheme-I**).

The urease enzyme is also pivotal in the hydrolysis of 30% of the total urea production in the human gastrointestinal tract [21]. Moreover, bacterial urease activity, after urea cleavage in saliva, helps in preventing dental cavities by elevating pH [22]. *Helicobacter pylori*, a microaerophilic pathogen, is responsible for urinary [23] and gastrointestinal infections [24], including those in humans [25]. *H. pylori* can survive within a limited pH range (4.0-8.2) during colonization in the human stomach [26]. Its survival in the low pH conditions of stomach is attributed to the elevation of pH in its microenvironment due to the production of ammonia through urease enzyme

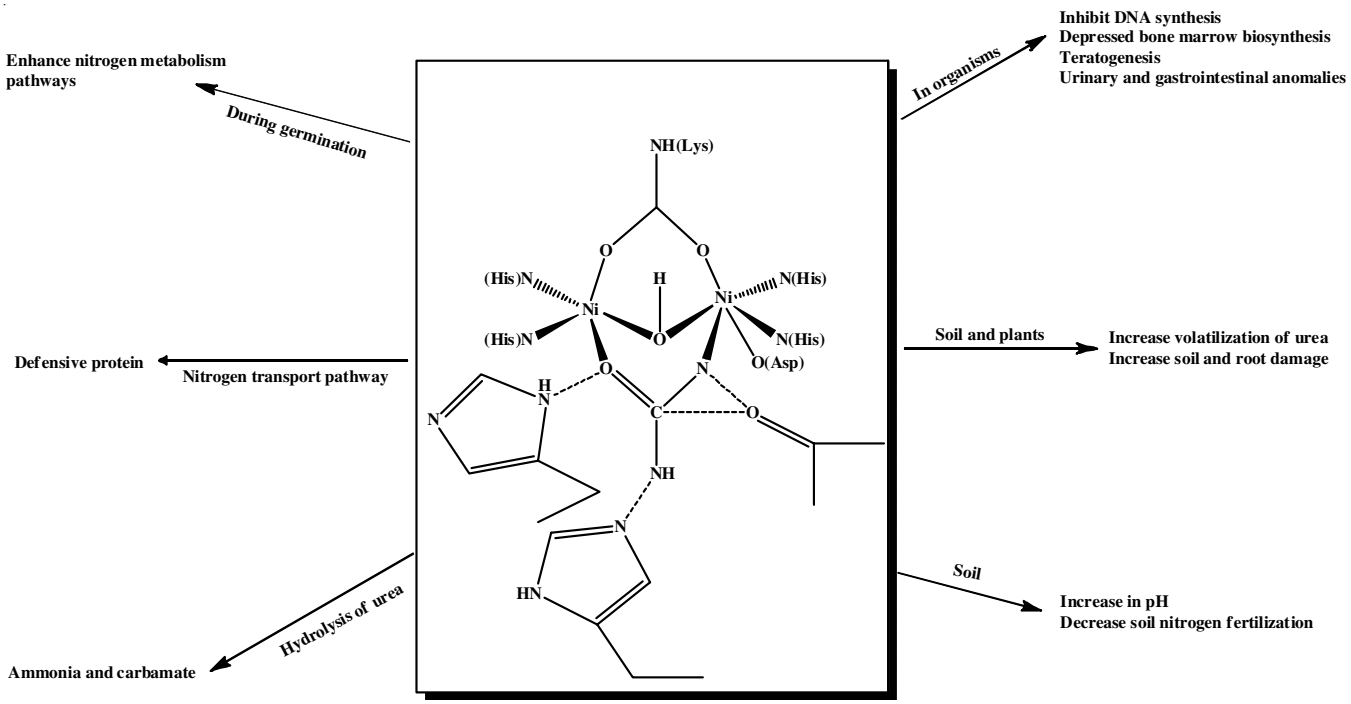
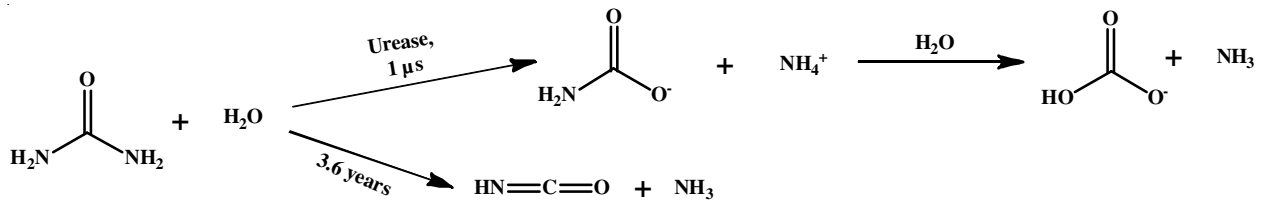


Fig. 1. Urease enzyme structure and some positive and negative implications of ureae



Scheme-I: Urease catalyzed hydrolysis of urea

activity. Consequently, the production of urease by the bacterium poses significant health risks in the urinary and gastrointestinal tracts, such as kidney stone formation [27], hepatic encephalopathy [28], hepatic coma [29,30], pyelonephritis, urolithiasis [31] and urinary catheter encrustation [32,33]. Urease inhibitors are extensively employed to mitigate the adverse effects of urease enzymes [34], thereby serving as effective antiulcer drugs [35] and enhancing nitrogen uptake in the form of urea by plants [36]. Therefore, urease inhibitors are garnering attention for their active role in reducing the activity of this enzyme [37,38].

Over the past four decades, global agricultural food production has increased seven-fold. The challenge for the upcoming decades is to develop highly productive agriculture while preserving environmental quality to meet the needs of the growing world population [39]. Schiff bases, also referred to as "privileged ligands," exhibit a wide range of biological activities, such as antifungal [40], antibacterial [41], anticancer [42], anti-inflammatory [43], trypanocidal [44], anti-HIV [45], antimalarial [46] and anti-urease properties. Due to the biological activity associated with the imine group in Schiff bases, significant research has been conducted on this moiety in the pursuit of creating novel bioactive molecules [47,48]. Schiff bases serve as versatile ligands capable of coordinating various metal ions in different coordination geometries and oxidation states [49]. Additionally, when incorporated with certain transition, alkali and alkaline earth metals, Schiff bases produce variable urease inhibitory activity. Transition metal complexes of Schiff bases have been identified for their ability to mitigate the adverse effects of urease enzymes. In this review, we highlight the significant contributions made by various research groups worldwide in the synthesis and activity evaluation of Schiff bases and their metal complexes in urease inhibition.

Compound classes as urease inhibitors: Various classes of compounds have been extensively explored for their efficacy in inhibiting urease activity, as depicted in Fig. 2. These inhibitors can be broadly classified into two main categories.

Organic compounds constitute one category and encompass acetohydroxamic acids [50], humic acid [51] and 1,4-benzoquinone [52,53], along with α-hydroxyketones [54]. On the other hand, inorganic inhibitors include heavy metal ions [55,56] such as zinc(II), cadmium(II), magnesium(II), copper(II) [57-61], boric acid [62] and fluorides [63]. A diverse array of compound classes, as illustrated in Fig. 2, have been utilized for urease inhibition. Notable among these are hydroxamic acids, widely recognized as some of the most effective urease inhibitors [64,65] and phosphorous compounds, particularly phosphoramidates [66], which have demonstrated remarkable efficacy.

Polyphenols, exemplified by gallocatechin [67], have also emerged as effective urease inhibitors. Similarly, flavonoids like quercetin [68] have been identified for their inhibitory effects

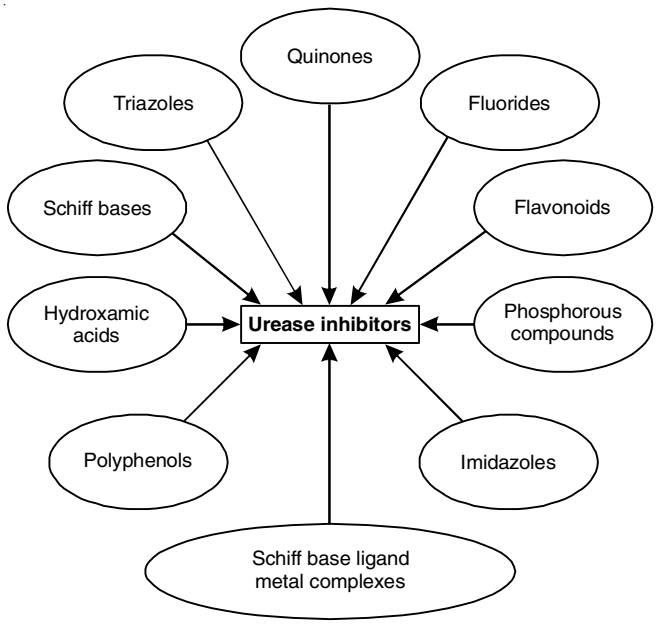


Fig. 2. Major compound classes as urease inhibitors

on urease activity. Additionally, certain triazoles [69] and imidazoles [70-72] have shown promise as potent anti-urease agents. Moreover, fluoride ions [73] and Schiff bases represent distinct classes of compounds recognized for their inhibitory effects on urease activity. Notably, metal complexes containing Schiff base ligands have attracted significant attention in the scientific community due to their potential as urease inhibitors. Further investigation into the synthesis of such compounds is warranted to develop more potent urease inhibitors with enhanced safety, bioavailability and reduced toxicity, making them an attractive target for researchers. Recent hypotheses suggest that certain transition metal complexes with Schiff bases may possess urease inhibitor activity [74]. In the following sections, we will explore the urease inhibitory activity of Schiff bases and their transition metal complexes as reported in the literature.

Schiff bases and their use as urease inhibitors: Schiff bases, organic compounds first reported by Hugo Schiff in 1864 [75], feature a versatile pharmacophore comprising the imine (**1**) or azomethine (**2**) functional group (-C=N-) as shown in Fig. 3 [76]. These compounds are synthesized through the condensation of aldehydes (**3**) and primary amines (**4**), typically utilizing organic solvents like methanol, THF and DCE (**Scheme-II**).

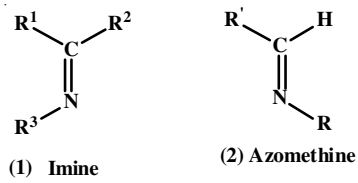
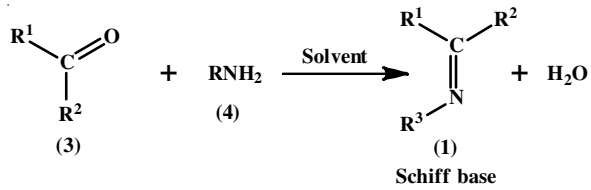


Fig. 3. General structure of a Schiff base



Scheme-II: Synthesis of Schiff base

Schiff bases are widely known for their many uses, spanning biological [77], clinical [78], analytical & industrial [79] and catalysis [80], which include pigments, dyes and organic synthesis [81]. They also play essential roles in enhancing the stability of catalysts, both homogeneous and heterogeneous, as well as in analytical and magneto-structural chemistry, luminescent probes, agrochemicals and biological agents [82-84]. In medicinal chemistry, Schiff bases and their metal complexes are highly valued due to their diverse biological functions. These include their ability to combat bacteria, viruses, fungi, parasites, tumors, HIV, protozoa and helminths [85-87]. Notable examples of Schiff base derivatives with distinct biological activities include ancistrocladidine (**5**), having antimalarial activity [88], synthetic Schiff base *N*-(salicylidene)-2-hydroxyaniline (**6**) as antibacterial activity [89] and natural product derived compound *e.g.* chitosan-derived Schiff bases (**7**) as antifungal agent [90] (Fig. 4).

Various research groups have reported a broad spectrum of Schiff bases, which have been extensively evaluated for their

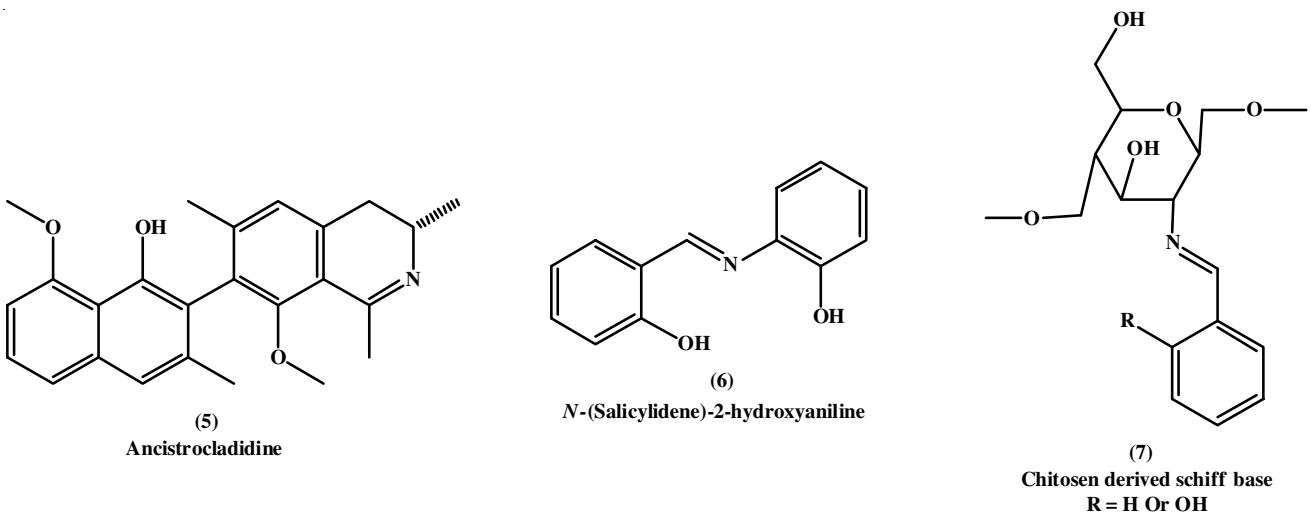


Fig. 4. Structure of Schiff base derivatives

ability to inhibit urease activity. For instance, Aslam *et al.* [91] synthesized semicarbazide hydrazones (**10**) derived from thiosemicarbazide (**8**) and various aromatic aldehydes (**9**) (**Scheme-III**) and subsequently assessed their inhibitory effects on jack bean urease. To gauge the potency of these compounds, urea was employed as a reference. Generally, aromatic rings bearing electron-withdrawing groups exhibited heightened inhibition. Molecular docking studies unveiled interactions between the enzyme's metal center (Ni) and the sulfur atom within the Schiff base, with observed hydrogen bonding involving residues Arg439 and Cme592 with the O- of the NO_2 group.

Thiazole derivatives, owing to their antimicrobial and diverse biological activities, have attracted significant interest within the scientific community. Recently, Schiff bases derived from thiazoles have emerged as a novel class of urease inhibitors. Chaudhary *et al.* [92] presented a series of potent urease inhibitors based on Schiff bases of thiazoles (**11**), while Saeed *et al.* [93] described the inhibitory activity of thiosemicarbazide derivatives against jack bean urease (Fig. 5). Their synthesized thiosemicarbazide (**12**) and thiosemicarbazide Schiff base, 2-{hetero(aryl)methylene}hydrazine-1-carbothioamides (**13**), demonstrated notable inhibitory effects, with compounds bearing smaller heterocycles exhibiting enhanced potency, particularly those incorporating a furan ring (compound **13**).

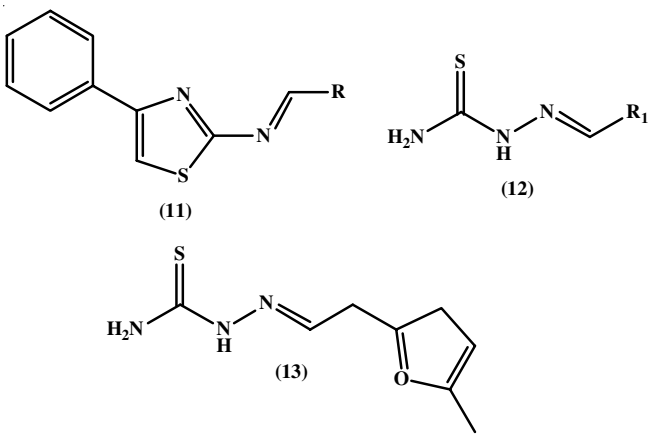


Fig. 5. Schiff base of thiazole ligand and thiosemicarbazide derivatives

The diverse applications of 1,2,4-triazole containing compounds in medicinal chemistry acting as medication for anticancer [94,95], anti-inflammatory [96], antidiabetic [97], antimalarial [98], antiproliferative [99], antimitotic, anti-vascular [100], anticonvulsant [101], antifungal purposes and displaying enzyme inhibition potential like urease [102] and α-fucosidase [103], there has been a growing interest in synthesizing and assessing triazole-based Schiff bases for their ability to inhibit urease. Rafiq *et al.* [104] conducted a study where they synthesized a series of triazole-based Schiff bases (**14**,**15**) (Fig. 6) and evaluated their effectiveness in inhibiting urease. All the synthesized bases proved to be more potent inhibitors of urease compared to thiourea.

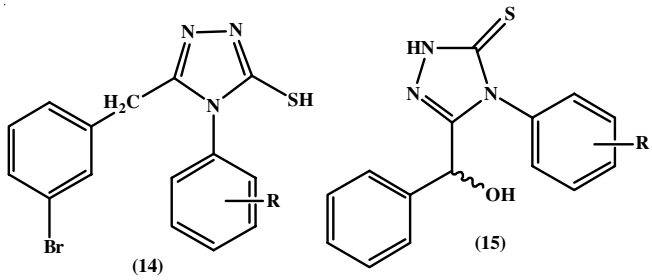


Fig. 6. 1,2,4-Triazole based Schiff bases as urease inhibitors

Nitrogen-containing benzimidazoles and sulphadiazine (Fig. 7) exhibit a range of biological activities and hold potential as drug candidates for the pharmaceutical industry. Aman *et al.* [105] synthesized derivatives of chiral benzimidazoles (**16**) and assessed their inhibition activity against jack bean urease. There has been a vision to incorporate this moiety into the sulfonamide class of drugs. Additionally, Hamad *et al.* [106] synthesized a series of Schiff base derivatives of drug sulphadiazine (**17**) and evaluated their antiurease activity.

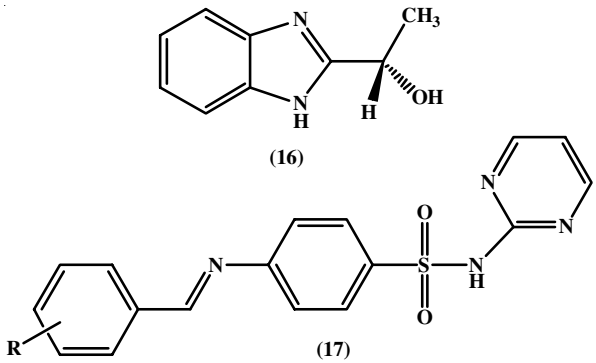
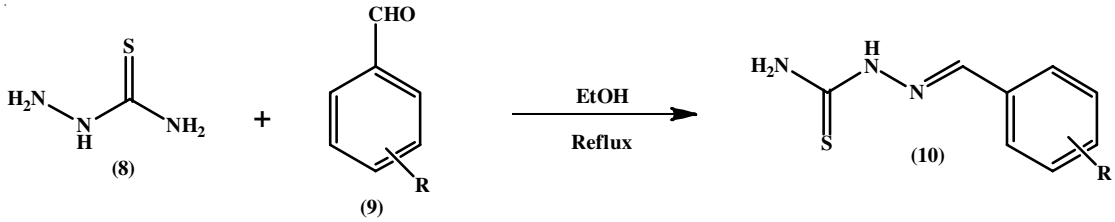


Fig. 7. Schiff bases of benzimidazoles and sulphadiazine drug

The heterocyclic compound, isatin, is an indole derivative that plays a significant role in the synthesis of medicines. Isatin derivatives' Schiff bases have shown effectiveness against microorganisms [107,108] and possess notable antiviral, antibacterial and antifungal properties [109]. Consequently, Aziz *et al.* [110] synthesized two new isatin derivatives, (1-allyl-2-oxo-indolin-3-ylidene)-4-methylbenzenesulfonohydrazide (**18**) and (1-allyl-2-oxoindolin-3-ylidene)-4-chlorobenzenesulfonohydrazide



Scheme-III: Synthesis of [1-(substituted benzylidene)thiosemicarbazides] derivatives

(**19**) (Fig. 8) and tested their urease inhibition activity on the urea enzyme of *Bacillus pasteurii*, achieving excellent yields.

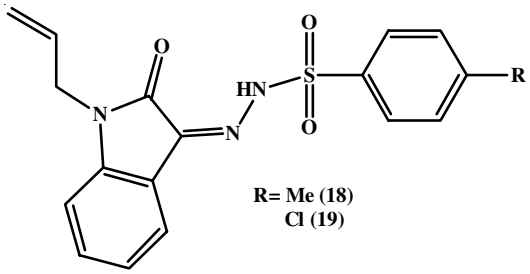


Fig. 8. Isatin derivatives as a Schiff base

Schiff base metal complexes in urease inhibition: Currently, the transition metal-based drugs are captivating the scientific community due to the pivotal role of metals in the biological processes, occupying crucial positions in enzymes and serving as catalysts. Furthermore, they hold significance in redox enzyme systems and bioinorganic chemistry owing to their reduced toxicity, target specificity, high pharmacological effectiveness and capacity for non-covalent DNA binding. The versatility of transition metals, characterized by their multitude of reactive sites, has inspired the synthesis of transition metal complexes for designer metallonucleases [111]. For instance, cisplatin, a chemotherapy drug based on platinum, was researched by Rosenberg *et al.* [112] for its anticancer properties and remains in use against various cancers including testicular, ovarian, bladder, cervical, lung and brain tumors.

Heavy metals, especially Ag^+ and Hg^{2+}, are known to inhibit urease, although other heavy metals also exhibit urease inhibition [113]. Relative urease inhibition order of transition metals is:

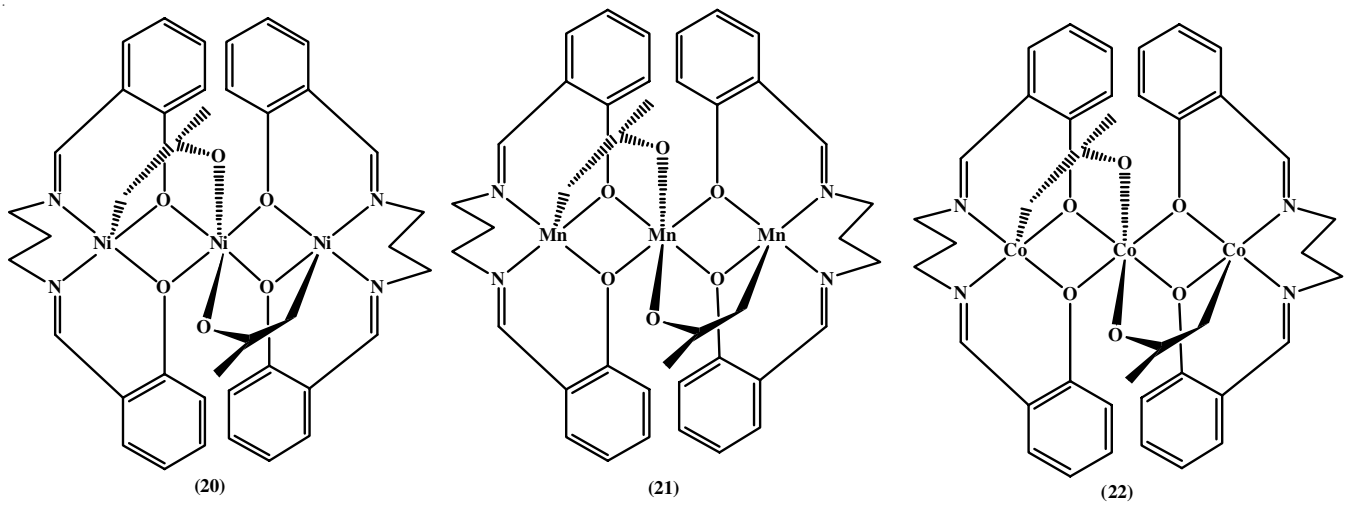
$$Ag^+ = Hg^{2+} > Cu^{2+} > Ni^{2+} > Cd^{2+} > Zn^{2+} > Co^{2+} > Fe^{3+} > Pb^{2+} > Mn^{2+}$$

Transition metals are integral to various metalloenzymes responsible for metabolic processes. Consequently, coordination compounds are increasingly being evaluated for their ability to modulate the functioning of natural metal ions within living organisms. Copper(II) complexes with Schiff bases, owing to the well-established role of copper(II) in biological systems, exhibit potent anti-urease activity and have been extensively synthesized and evaluated by researchers worldwide. Shi *et al.* [114] reported transition metal complexes with nickel(II) (**20**), manganese(II) (**21**) and cobalt(II) (**22**) (Fig. 9) using ecofriendly, inexpensive and commercially available reagents. Metal acetates were reacted with *N,N′-bis*(salicylaldehyde)-1,3-propanediamine (SALPD) and *N,N′-bis*(2-hydroxynapthylmethenylimine)-1,3-propanediaminate (NAPTPD). These Schiff base transition metal complexes displayed urease inhibitor activity against jack bean urease. Notably, the complexes derived from nickel and manganese showed greater inhibitory properties than standard acetohydroxamic acid.

Li *et al.* [115] reported the synthesis of Schiff base transition metal(II) complexes (**23**) [Cu(II)] from Schiff base ligands derived from condensation of salicyaldehyde with glycine, *N*-(2-aminoethyl)morpholine, 4-(2-aminoethyl)phenylic acid and 4-(2-aminoethyl)benzsulphamide with transition metals. These complexes exhibited significant urease inhibition activity (Fig. 10). Chen *et al.* [116] synthesized a series of Schiff base transition metal complexes (**24**) from Schiff base ligands obtained by reacting 3,5-dibromosalicyaldehyde with 2-chlorobenzylamine, benzylamine, cyclohexylamine and *N,N′*-dimethylethylenediamine with Cu(II) metal (Fig. 10). Docking studies of these complexes revealed strong interaction between enzyme and complexes, explaining their strong inhibition activity against urease.

Isatin derived thiosemicarbazones exhibit various biological properties, including antiulcer, antibacterial, antifungal, antineoplastic, antiviral, enzymatic inhibition [117,118]. Pervez *et al.* [119] synthesized a class of N4-subsituted isatin-3-thiosemicarbazone (**28**) from a common intermediate methyl-2-(2-oxo-1,2-dihydroxy-3*H*-indol-3-ylidene)-1-hydrazenecarbodithioate (**27**) and this intermediate was synthesized by condensation reaction of isatin (**26**) with methyl-1-hydrazinecarbothionate (**25**) followed by reaction with amine (**Scheme-IV**). These derivatives demonstrated cytotoxicity, antifungal, antibacterial and urease inhibitor activity.

Ara *et al.* [120] synthesized vanadium complex (**30**) from Schiff base hydrazide ligands (**29**) and vanadyl sulfate (**Scheme-V**), reporting urease inhibitory activity. The Schiff base ligands were synthesized from hydrazine hydrate and esters in ethanol.



(20) (21) (22)

Fig. 9. Nickel, manganese and cobalt based Schiff base metal complexes as synthesized by Shi *et al.* [48]

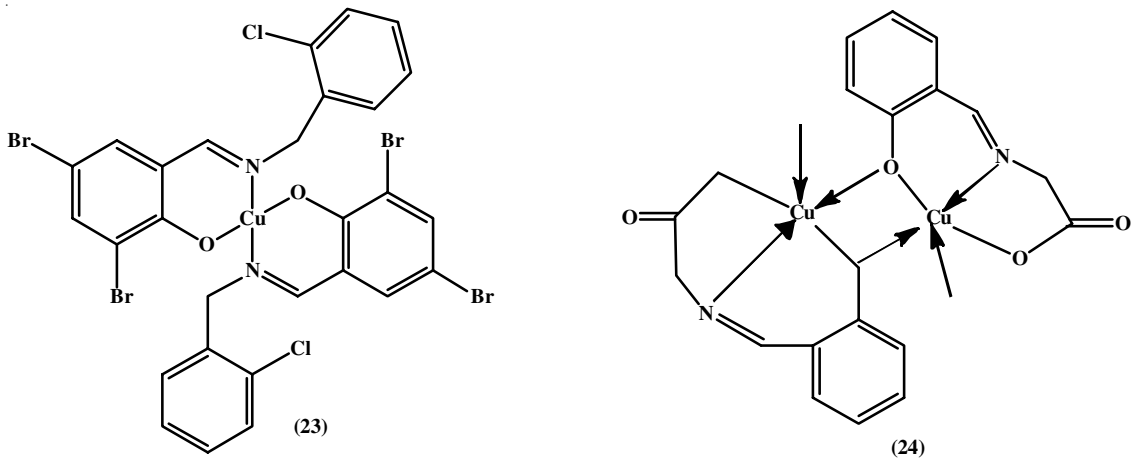
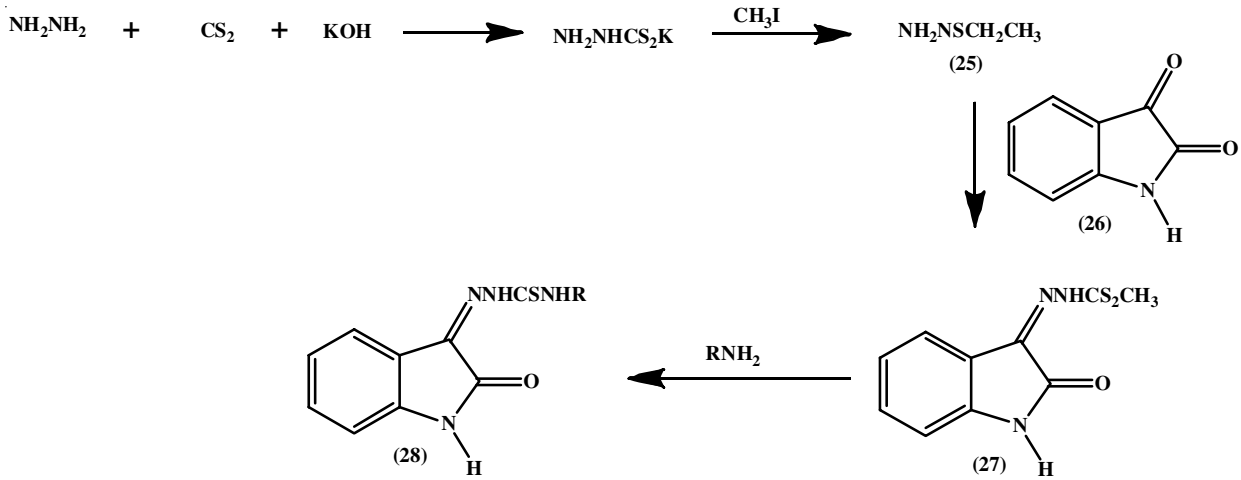


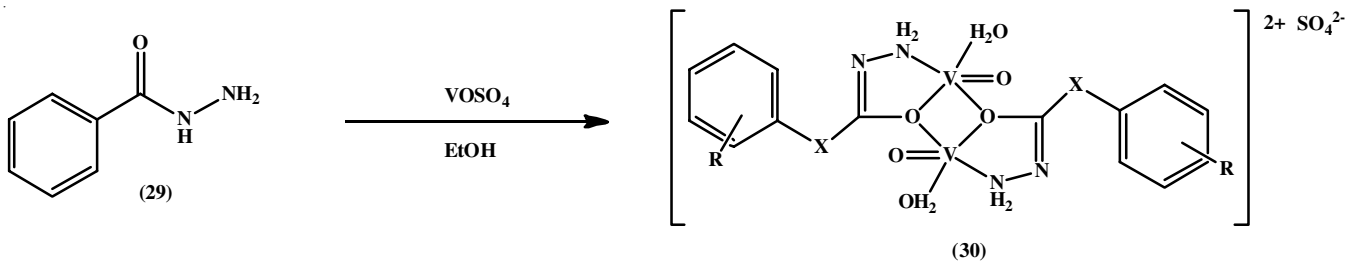
Fig. 10. Structure of transition metal complex with salicylaldehyde based Schiff bases



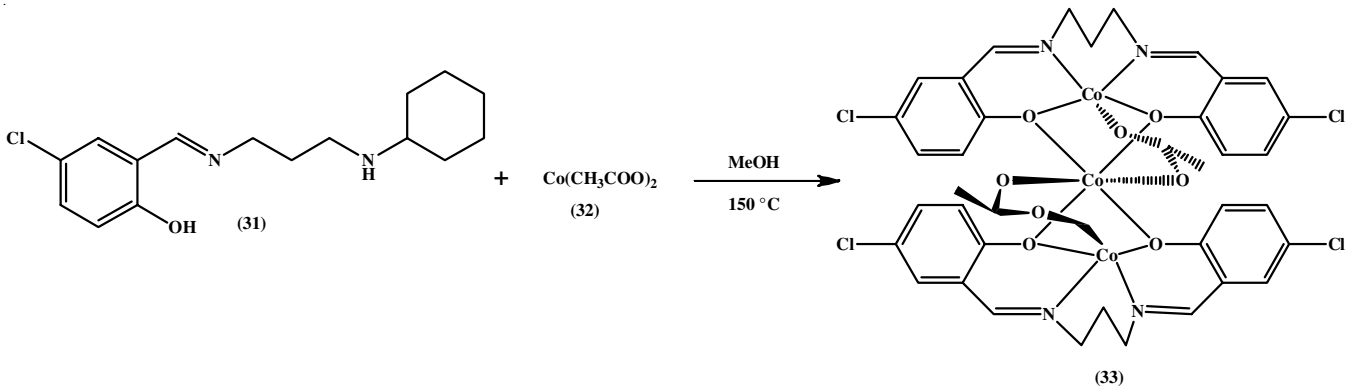
Scheme-IV: Isatin based thiosemicarbazone Schiff bases

The inhibitory activity of the metal complex was attributed to the vacant site in the pentacoordinated vanadium complex for coordination with the enzyme. Metal complexes with cobalt(II) and *bis*-Schiff base ligand *N,N′-bis*(5-chloro-salicylidene)-1,3-propanediaminate (CPDA) were reported by You & Zhou [121] and trinuclear cobalt(II) complex, $Co[Co(CH_3COO)(CPDA)]_2$ (**33**) were derived from the Schiff base ligand 4-chloro-2-[(3-cyclohexylaminopropylimino)methyl]phenol (CCP) (**31**) by reacting with metal salt (**32**), which is depicted in **Scheme-VI**. These complexes exhibited excellent urease inhibition against jack bean urease.

Wang *et al.* [122] reported the synthesis, characterization and urease inhibitory activity of two copper complexes *viz.* $[CuBrL_1]$ and $[CuBrL_2]$ derived from Schiff bases *e.g.* 1-[(2-diethylamino-ethylimino)methyl]naphthalen-2-ol (**34**) and 2,4-dibromo-6-[(2-diethylaminoethylimino)methyl]phenol (**35**) (Fig. 11). Both complexes showed greater urease inhibition compared to the Schiff bases and corresponding organic inhibitors (acetohydroxamic acids) [123]. You *et al.* [124,125] reported the synthesis of azide-bridged zinc complexes from tridentate Schiff base ligands (**36** and **37**) but their complexes have weak urease inhi-bition activity. In a subsequent study, same group reported Schiff base copper(II) complexes and eight Cu-Zn heterodinuclear complexes, which showed strong anti-urease activity (Fig. 12).



Scheme-V: Hydrazide ligands used in the synthesis of vanadium(IV) complexes



Scheme-VI: CPDA-based cobalt(II) complex

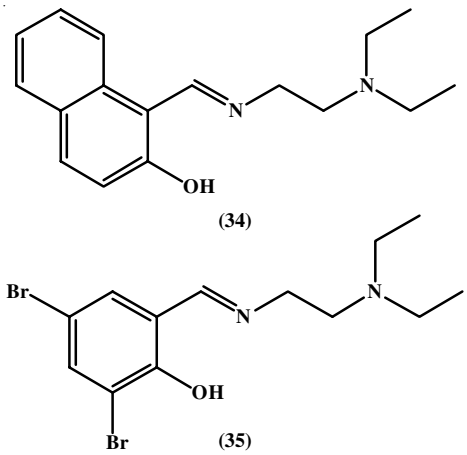


Fig. 11. Schiff base ligands for complexation with copper as elucidated by Wang *et al.* [122]

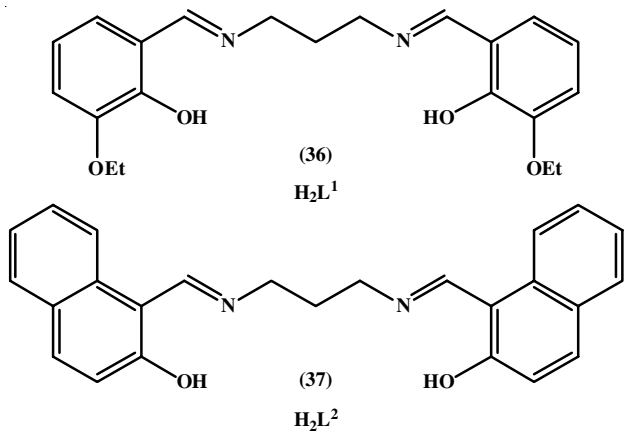


Fig. 12. Few Schiff bases used for complexation with metals by You *et al.* [124,125]

The Schiff base manganese complexes exhibit catalytic activity [126-129] and form polymeric structure through thiocyanato ligand. Recent studies indicated that Cu(II), Cd(II), Co(II,III) and Ni(II) complexes with Schiff base ligands display urease inhibitor activity. Inspired by these findings, Zhang *et al.* [130] synthesized thiocyanato-bridged polymeric Schiff base manganese(II) complexes (**41**) from Schiff base ligands derived from 4-methoxysalicyaldehyde with *N*-ethylethane-1,2-diamine and 3-ethoxysalicyaldehyde with *N*-(2-hydroxyethyl)-ethane-1,2-diamine, followed by reaction with ammonium thiocyanato (**40**) and manganese salt (**39**) (**Scheme-VII**). While Schiff base ligands and Mn(II, III) salts individually did not exhibit urease inhibitor activity [131], Schiff base Mn(III) complexes showed moderate inhibition activity against urease. It was also observed that Schiff base manganese complexes displayed significant urease inhibitor activity against *H. pylori*. Structure-activity relationship (SAR) studies of these complexes revealed that the alkoxy group did not participate in urease inhibition, whereas coordinated water molecules played a significant role in inhibition through hydrogen bonding.

Cui *et al.* [132] synthesized new Schiff base transition metal complexes (**46**) by reacting primary amines (**44**) with 3,5-dibromosalicyaldehyde or 3,5-dichlorosalicyaldehyde (**43**) and metal salts of Cu(II), Ni(II), Zn(II) and Co(II) (**Scheme-VIII**). It was observed that synthesized Schiff base copper(II) complexes exhibited stronger urease inhibition against jack bean urease. Docking studies also suggested that Schiff base copper(II) complexes hold promise as future urease inhibitors. Lu *et al.* [133] reported the synthesis of three new metal complexes of Ni(II), Zn(II) and Co(II) with hydroxy group rich Schiff bases (**47**) *e.g.* 2-{[1-(5-chloro-2-hydroxyphenyl)methylidene]-amino}-2- methylpropane-1,3-diol (HL_1), 2-{[1-(2-hydroxy-3-methoxyphenyl)methylidene]amino}-2-ethylpropane-1,3-diol (HL_2) and 2-{[1-(5-bromo-2-hydroxy-phenyl)methylidene]-amino}-2-methylpropane-1,3-diol (HL_3) (Fig. 13). All these Schiff bases are multidentate ligands and form dicoordinated metal complexes. The resultant complexes were then evaluated for their anti-urease activity. The Schiff bases showed significant urease inhibitory activity, while the metal complexes were comparatively less active against *H. pylori* urease. Overall, both Schiff base and complexes exhibited lower activity than the standard acetohydroxamic acid. The general formula of the synthesized metal complexes was $[M(L)_2]\cdot H_2O$. Molecular

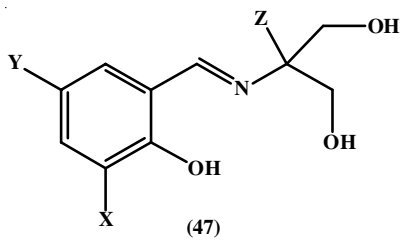
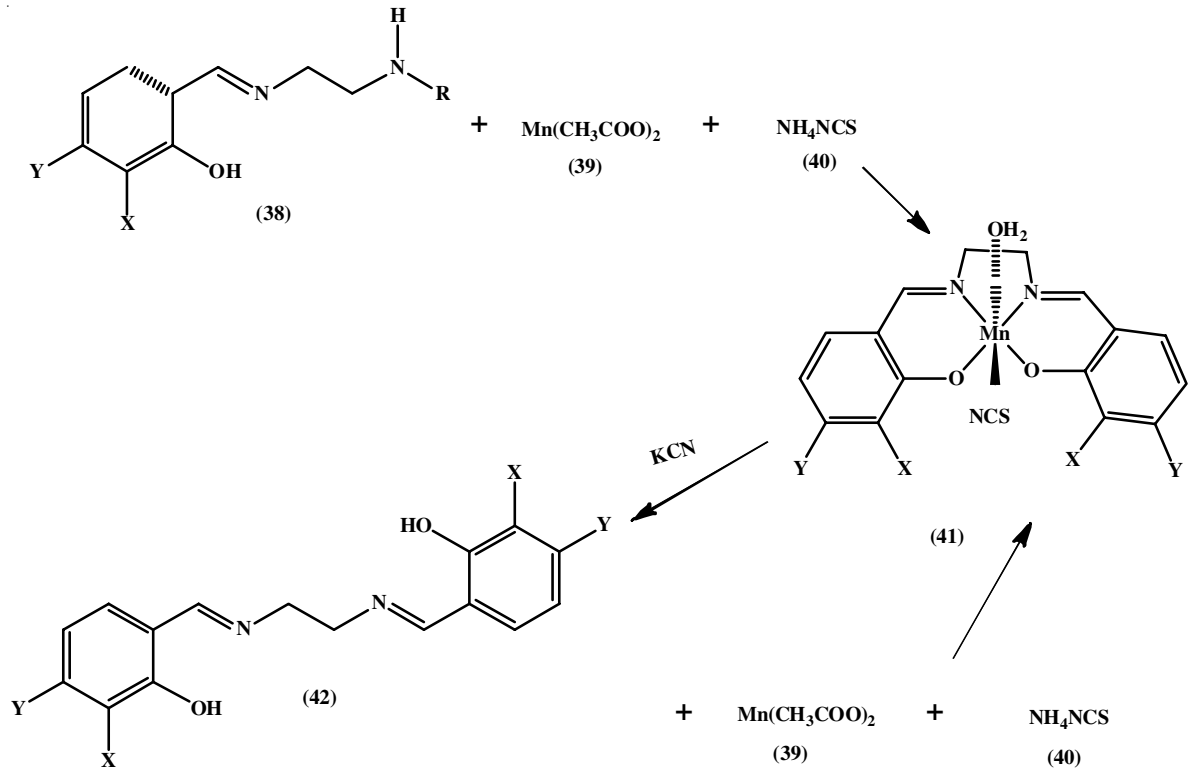
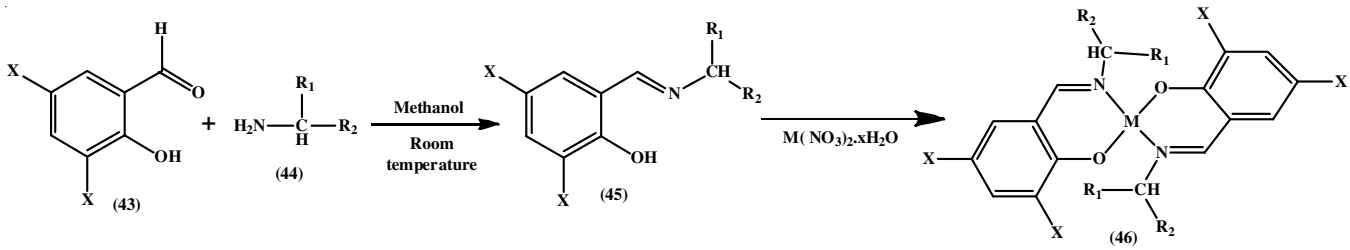


Fig. 13. General structure of hydroxy rich Schiff base



Scheme-VII: Thiocyanate bridged manganese(II) Schiff base complexes



Scheme-VIII: Synthesis of transition metal complexes [Cu(II), Ni(II), Zn(II) and Co(II)]

docking studies revealed that the bulkiness of the large complexes prevented them from properly fitting into the active enzyme pocket, resulting in lesser activity against urease inhibition compared to standard acetohydroxamic acid.

Kharat *et al.* [134] reported distorted trigonal bipyramidal zinc(II) complexes (**48**) from substituted terpyridine, chloride and bromide Schiff base ligands and their structure were elucidation by X-ray crystallography (Fig. 14). The metal complexes exhibited moderate inhibitory activity against jack bean urease. Li *et al.* [135] reported four Schiff base transition metal complexes $[Cu(L)(phen_2)]\cdot C_2H_5OH$, $[Zn(L)(phen)_2]\cdot C_2H_5OH$, $[Ni(L)(phen)_2]\cdot C_2H_5OH$ and $[Co(L)(phen)_2]\cdot C_2H_5OH$ [L=1-{(2-hydroxynaphthalin-1-yl)methylene}thiosemicarbazide (**49**) and phen = 1,10-phenanthroline], which were synthesized from Schiff base ligands derived from the condensation of 2-hydroxy-1-naphthaldehyde with thiosemicarbazide and $M(OAc)_2$ (M = Cu, Zn, Ni, Co). These compounds were investigated for their fluorescent and urease inhibitory potential (Fig. 14).

Li *et al.* [136] reported two Schiff base copper(II) complexes (**50**) synthesized from Schiff base derived from 5-chlorosalicylaldehyde and 4-methoxysalicylaldehyde and evaluated them

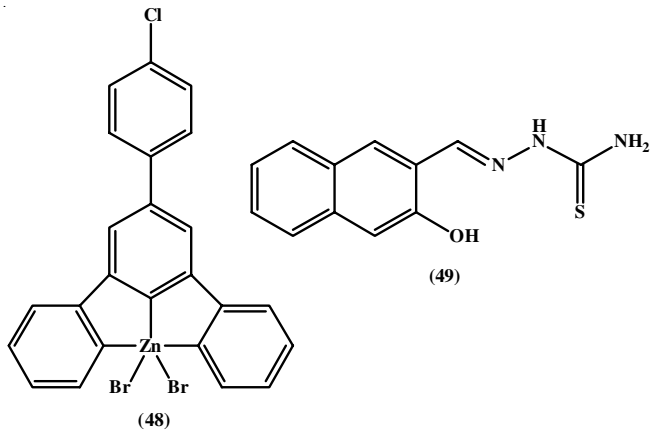


Fig. 14. Terpyridine based zinc metal complex and thiosemicarbazide Schiff base

for their urease inhibitory activity (Fig. 15). Schiff bases were prepared from the condensation of 5-chlorosalicylaldehyde and 4-methoxysalicylaldehyde with *n*-butylamine in methanol with a yield of up to 89%. The Schiff base copper(II) complexes, *bis*(*N*-*n*-butyl-5-chlorosalicylaldiminato) copper(II) and

bis(*N*-*n*-butyl-4-methoxysalicylaldiminato) copper(II), were synthesized using Schiff base derived from 5-chlorosalicylaldehyde and 4-methoxysalicylaldehyde with the corresponding copper(II) salts. *Bis*(*N*-*n*-butyl-5-chlorosalicylaldiminato)-copper(II) complex exhibited a distorted square-planar geometry, while *bis*(*N*-*n*-butyl-4-methoxysalicylaldiminato)-copper(II) displayed square planar geometry. Both copper(II) complexes exhibited strong urease inhibition activity compared to the acetohydroxamic acid standard. In 2015, Li *et al.* [137] synthesized two silver(I) complexes (**51**) with Schiff base ligands derived from 1,4-benzodioxane-6-carboxylic acid and 4,4′-bipyridine (Fig. 15). Both complexes were evaluated for anti-urease activity and found to be potent inhibitors of jack bean urease.

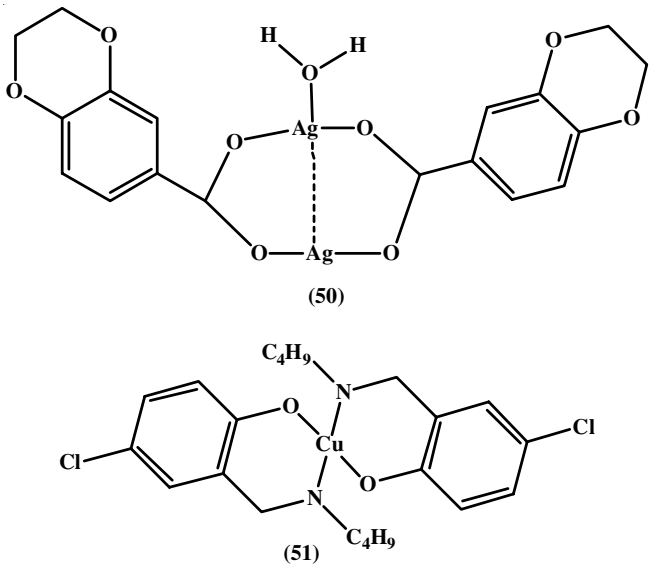


Fig. 15. Urease inhibiting dinuclear silver(I) and copper(II) complexes derived from Schiff base

Ikram *et al.* [138] reported the synthesis and urease inhibitory activity of metal complexes (**53**) of Co, Ni, Cu and Zn with salicylaldehyde based Schiff base ligands *viz*. 2-{(*E*)-[(4-chlorophenyl)imino]methyl}phenol (CIMP) and 2-{(*E*)-[(4-bromophenyl)imino]methyl}phenol (BIMP) (**52**) (**Scheme-IX**). Urease inhibition was evaluated against jack bean urease. Among all the complexes evaluated, copper complexes were found to inhibit the urease enzyme activity, attributed to the interaction of copper with glycine residues present on the enzyme's surface. Gou *et al.* [139] reported the synthesis of two dimeric copper(II) complexes, $[Cu(C_9H_7NO_4)(Py)]_2{\cdot}2(CH_3OH)$, where Py = pyridine and $[Cu(C_{13}H_9NO_3)(H_2O)]_2$, with Schiff base ligands. The Schiff base ligands, HL_1 (**54**) and HL_2 (**55**), were synthesized starting from glycine, 2,4-dihydroxybenzaldehyde and 2-hydroxy-1-naphthaldehyde, respectively (Fig. 16). These synthesized complexes were then assessed for their urease inhibitory activity against jack bean urease and were found to exhibit moderate activity.

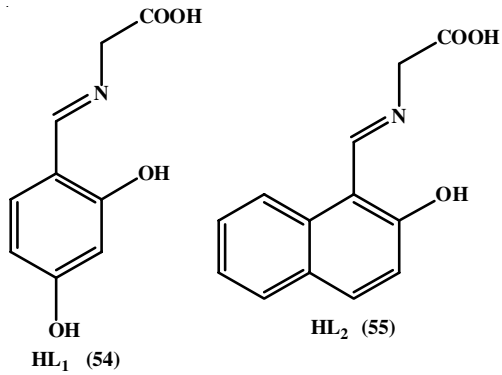
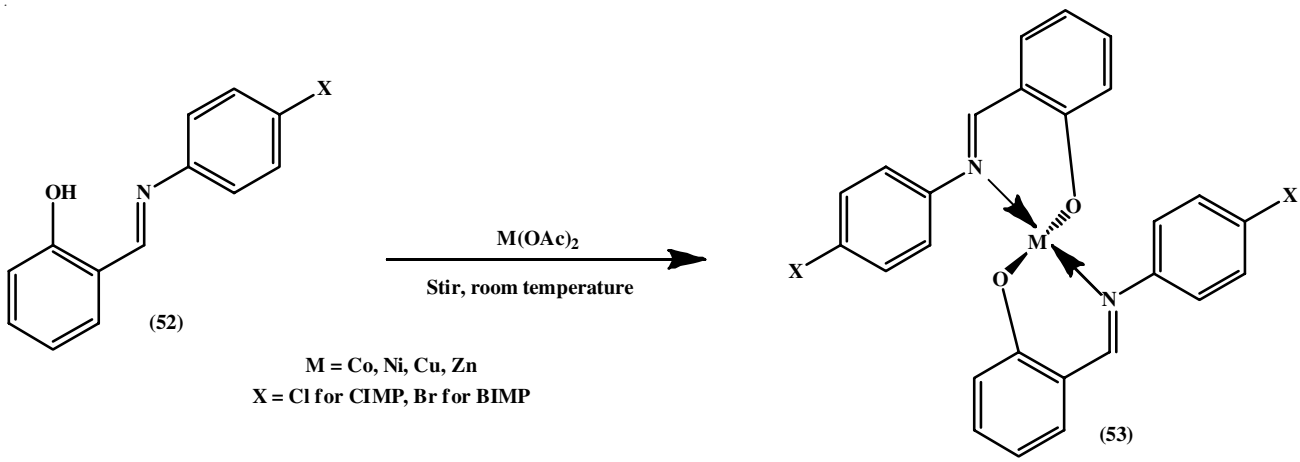


Fig. 16. Glycine and aromatic aldehyde-based Schiff bases

Jing *et al*. [126] investigated the Schiff base ligands *N*′-(2-hydroxy-5-methoxybenzylidene)-3-methylbenzohydrazone, 2-[(2-dimethylaminoethylimino)methyl]-4-methylphenol, *N*′-(2-hydroxybenzylidene)-3-hydroxybenzohydrazide and *N,N*′-*bis*(5-methylsalicylidene)-O-phenylenediamine with Co(II) metal and identified them as potential urease inhibitory. It was observed during the investigation that complexes with a square planner geometry demonstrated excellent urease inhibitor activity. Consequently, Rauf *et al.* [128] suggested that square planar Ni(II) complexes (**58**) with *N,N,N*′-trisubsituted thiourea (**56**) exhibited stronger urease inhibition against the enzyme (**Scheme-X**).

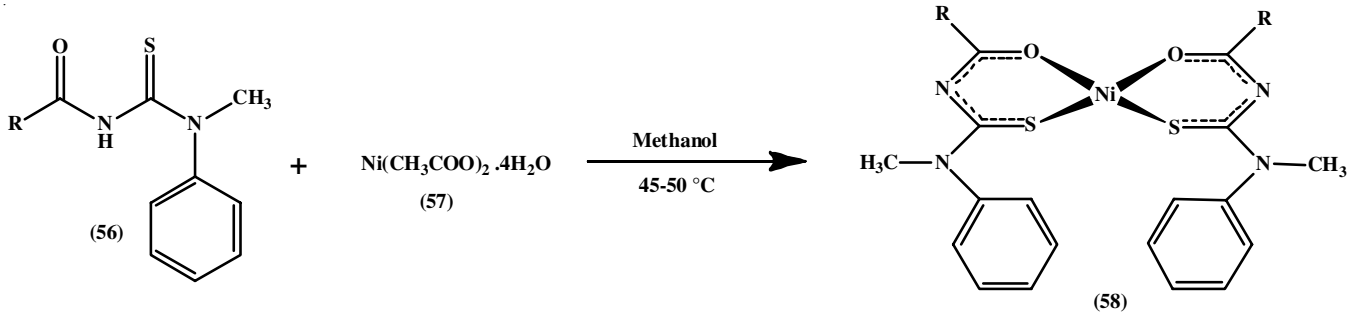
Xu *et al.* [140] reported copper(II), zinc(II) and iron(II) complexes derived from 1,2,4-triazolecarboxylic acid Schiff



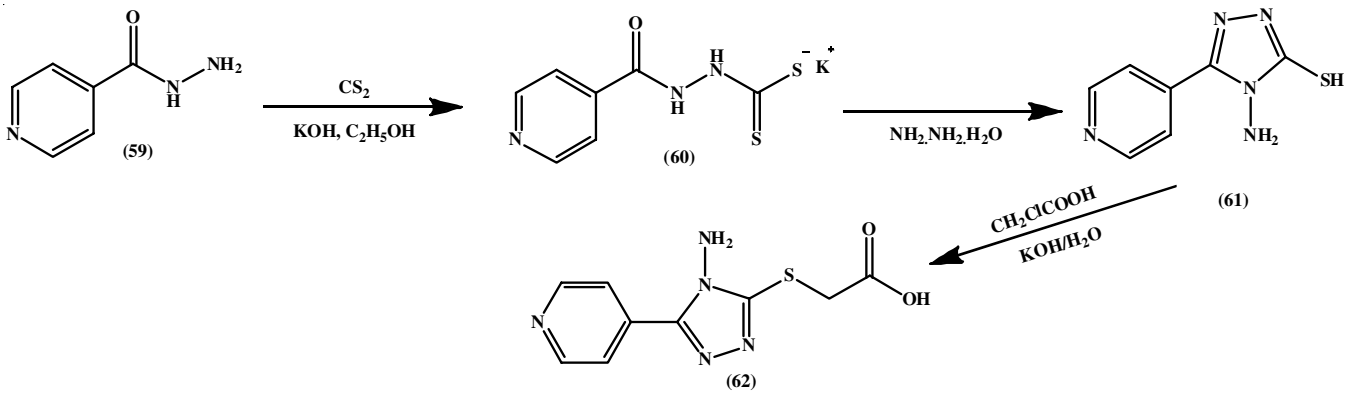
Scheme-IX: CIMP and BIMP based Schiff base metal complexes synthesized by Ikram *et al.* [138]

base ligands (**62**) (**Scheme-XI**) and the structures of these metal complexes were determined using X-ray crystallography. It was observed that copper(II) complexes displayed stronger enzyme inhibitory activity. Sangeeta *et al.* [141] synthesized Ni(II) and Cu(II) complexes of Schiff base ligands derived from 3,5-dichlorosalicylaldehyde (**63**) and *o*-anisidine (**64**) (**Scheme-XII**) and evaluated them for inhibitory activity against *H. pylori*. The complexes were prepared by addition of Schiff base ligand solution (**65**) to methanolic solution of nickel and copper salts ([$Ni(OAc)_2 \cdot 4H_2O$] and [$Cu(OAc)_2 \cdot H_2O$]). Strong inhibition was exhibited by complexes (**66**, **67**) (IC_{50} values for Ni and Cu complexes or 5.5 ± 2.0 µM and 4.2 ± 2.3 µM, respectively), compared to the Schiff bases and acetohydroxamic acid (28.1 ± 3.6 µM) [142].

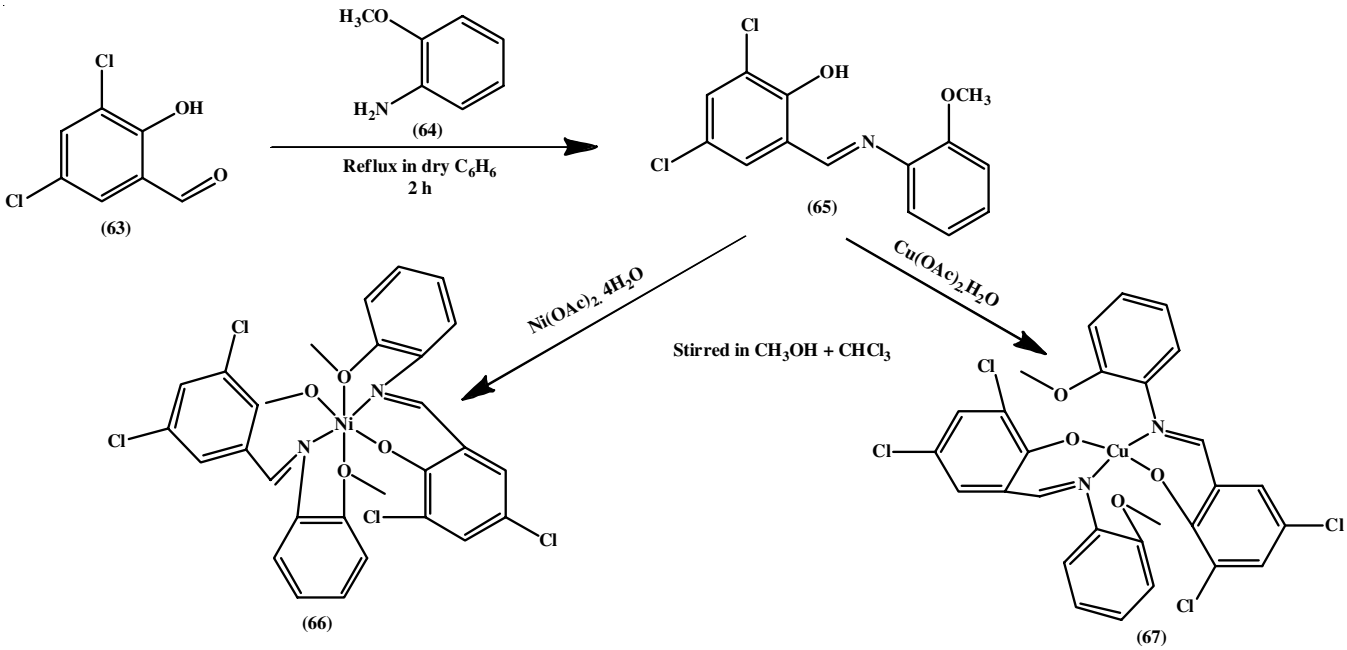
Continuing their research on isatin Schiff bases, Pervez *et al.* [143] synthesized copper(II) complexes of Schiff bases (**70**) of 5-(un)-substituted isatin (**69**) and 2,2- diphenylethanamine (**68**) by treating copper salt with the ligands, which were them-



Scheme-X: Synthesis of thiourea based Schiff base metal complex of nickel



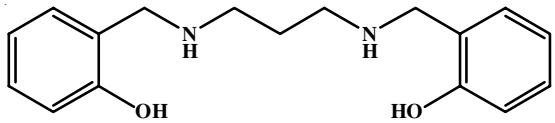
Scheme-XI: Synthesis of Schiff base ligand by Xu *et al.* [140]



Scheme-XII: Preparation of Schiff base ligand and metal complexes described by Sangeeta *et al.* [141]

selves prepared by reacting isatin with 4-methyl-*m*-phenylenediamine in ethanolic solution (**Scheme-XIII**). The metal complexes exhibited lesser activity against the urease enzyme than the Schiff base ligands. The most potent ligand with a bromo group exhibited an IC_{50} value of 0.04 ± 0.004 μM, which was more efficient than the standard, thiourea. The incorporation of metal ions with Schiff base ligands was found to diminish the anti-urease potential of the ligands. All the synthesized ligands as well as complexes were cytotoxic against observed cancer cell lines.

Schiff bases with reduced structure possess more stability than Schiff bases. Based on their stability and the known biological effects of copper complexes [144,145] on enzyme activity, Duan *et al.* [146] synthesized copper(II) complexes with reduced Schiff base ligand (**71**) and evaluated them for urease inhibitory activity (Fig. 17). The Schiff base ligand was synthesized from a methanolic solution of salicylaldehyde and 1,3-diaminopropane, which was then reduced with sodium borohydride. The synthesis of copper(II) complex occurred when the methanolic solution of copper perchlorate hexahydrate was mixed with a solution of reduced Schiff base in acetonitrile. The synthesized complexes were assessed for their anti-urease potential against acetohydroxamic acid as standard. The copper complex was found to have a square planar geometry, as confirmed by X-ray crystallography. The Schiff base was less potent than the complex for its anti-urease potential, with the complex an exhibiting IC_{50} value of 1.6 ± 1.2 μmol L^{-1}.

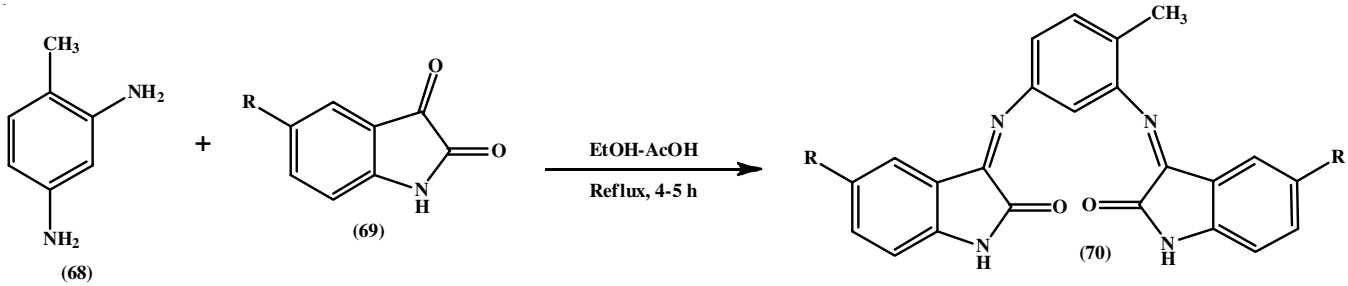


(71)

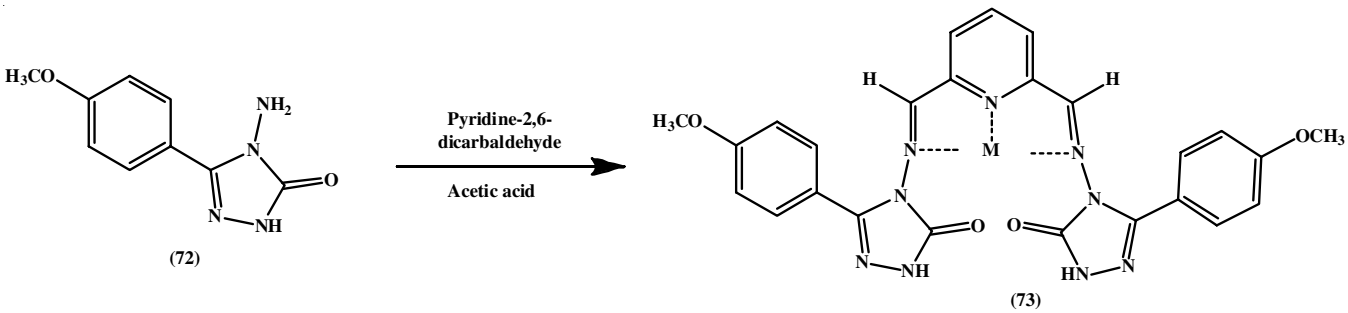
Fig. 17. Reduced Schiff base ligand

Hanif *et al.* [147] synthesized Schiff base derivatives containing two triazole rings arranged in a cage-like structure and investigated their urease inhibition activity. The Schiff base complexes (**73**) with two triazole ring were synthesized by reacting 4-amino-3-(4-methoxyphenyl)-1*H*-1,2,4-triazol-5(4*H*)-one (**72**) with pyridine-2,6-dicarbaldehyde in the presence of glacial acetic acid (3-4 drops) under reflux conditions for 8 h (**Scheme-XIV**). The starting material 4-amino-3-(4-methoxyphenyl)-1*H*-1,2,4-triazol-5(4*H*)-one was synthesized from 4-methoxybenzoyl chloride and carbohydrazide in dichloromethane followed by refluxing for 3 h. The synthesized compounds were evaluated for their inhibition of urease activity, revealing that the triazole cage containing oxygen and its metal complexes exhibited stringer inhibition compared to those containing sulphur and their corresponding metal complexes. Molecular docking studies indicated that copper complexes interacted strongly with jack bean urease and displayed favourable binding energy values.

Copper complexes with Schiff bases are renowned for their anti-urease properties. Continuing in this line of research, Wang *et al.* [148] synthesized copper(II) and zinc(II) complexes with Schiff bases (**76**) *viz.* 4-bromo-*N*′-(pyridin-2-ylmethylene)-benzohydrazide (HL_1) and 4-methoxy-*N*′-(pyridin-2-ylmethylene)benzohydrazide (HL_2). To synthesize the Schiff bases HL_1 and HL_2, 2-pyridinecarboxaldehyde (**74**) was refluxed in methanol with 4-bromobenzohydrazide and 4-methoxybenzohydrazide (**75**), respectively (**Scheme-XV**). The copper and zinc complexes, $[Cu(L_1)(NCS)(CH_3OH)]$ (**79**) and $[ZnCl_2(HL_2)]\cdot CH_3OH$ (**81**) were obtained by treating the Schiff base ligands HL_1 and HL_2 with copper perchlorate hexahydrate (**78**) and zinc chloride in methanol, respectively (**Scheme-XVI**). The structures of complexes were determined based on of IR and XRD data, revealing the square pyramidal geometry of copper complex,



Scheme-XIII: Synthesis of isatin Schiff base ligand

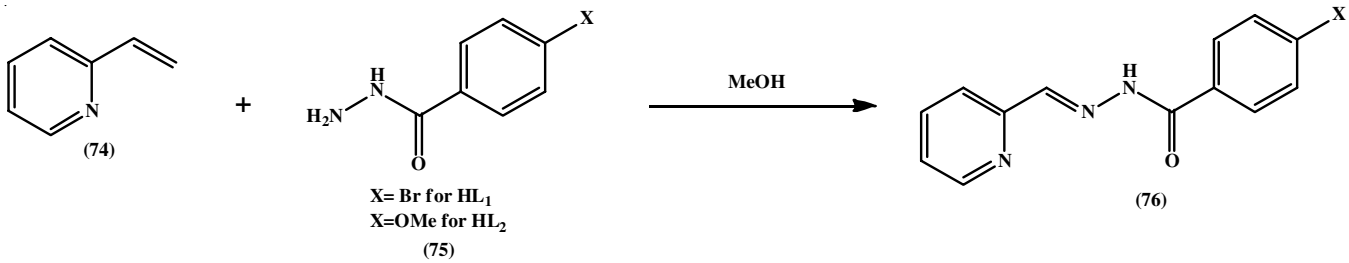


Scheme-XIV: Synthesis of two triazole ring bearing Schiff base complexes

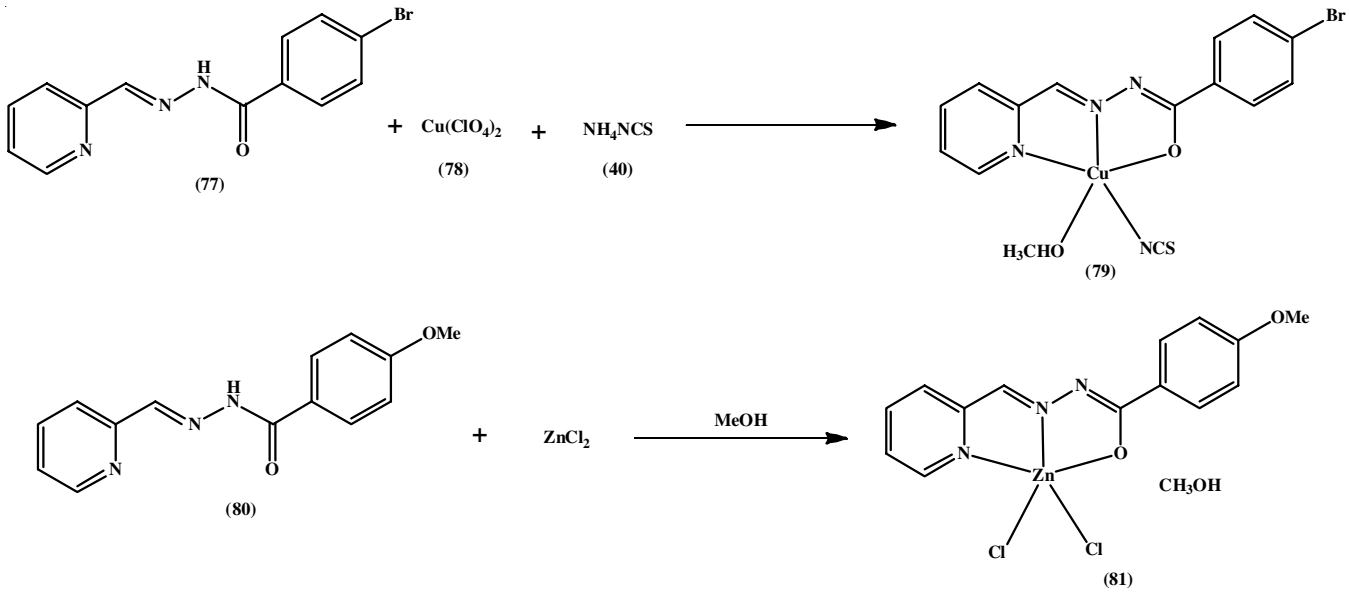
while the zinc metal atom exhibited trigonal bipyramidal geometry. The urease inhibition potential was evaluated against jack bean urease. The copper complex demonstrated strong inhibitory activity against the standard acetohydroxamic acid with IC_{50} value of 1.4 ± 0.8 μmol L^{-1}. However, the zinc complex and hydrazones exhibited lower potential for anti-urease activity.

Building on previous research regarding the efficacy of transition metal Schiff base complexes in urease inhibition by Wang *et al*. [149], they reported the synthesis and urease inhibitory activity of copper complexes with 5-methoxy-2-[(pyridin-2-ylmethylimino)methyl]phenol (HL′) (**84**) as the Schiff base ligand. The Schiff base ligand (HL′) was synthesized by reacting 4-methoxysalicylaldehyde (**82**) with 2-aminomethylpyridine (**83**) in the presence of methanol as a solvent (**Scheme-XVII**). Subsequently, the conversion of this Schiff base ligand into an azido-bridged dinuclear complex (**86**) occurred through its reaction with copper bromide and sodium azide in methanol at room temperature (**Scheme-XVIII**). The binuclear copper(II) complex exhibited excellent urease inhibition against jack bean urease with an IC_{50} value of 0.71 ± 0.32 mmol L^{-1}, which was more efficient compared to the standard acetohydroxamic acid drug. However, the Schiff base ligand itself was not active against urease.

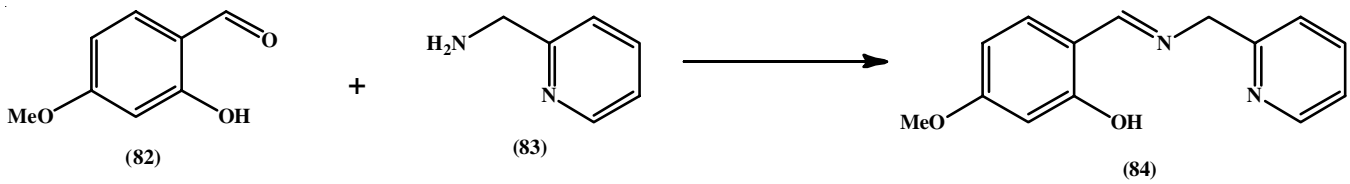
Zinc(II) based transition metal complexes are significant in urease inhibition due to their biocompatibility and lower toxic toxicity compared to other heavy metals. Therefore, Nayab *et al.* [150] reported synthesis of Zn(II) complexes containing thiophenyl and furyl based chiral amines and screened the synthesized compounds for their anti-urease activity against jack bean urease and bacterial urease (**Scheme-XIX**). The Zn(II) chloride complex, (*R*)-1-phenyl-*N*-(thiophen-2-ylmethyl)ethanamine Zn(II) chloride (**89**), [$LAZnCl_2$], was synthesized by reacting (*R*)-1-phenyl-N-(thiophen-2-ylmethyl)ethanamine (**88**) with $ZnCl_2$ in ethanol and these Zn(II) complexes significantly inhibited the tested enzymes. Molecular docking studies revealed that the methyl substituents enabled thiophenyl moiety to interact closely with the amino acid residues at the enzymes active sites.



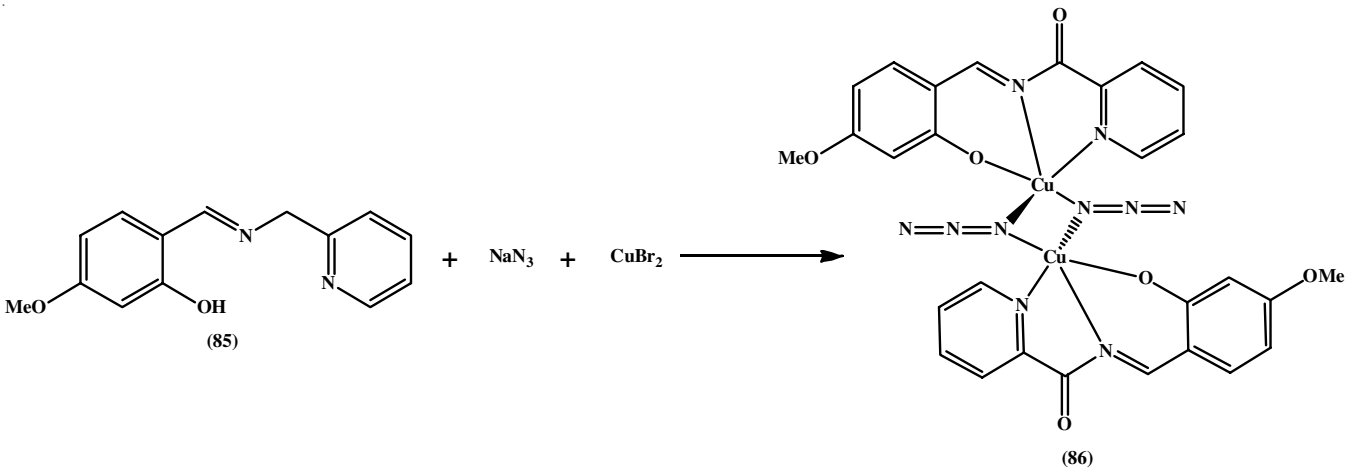
Scheme-XV: Synthesis of hydrazide based Schiff bases



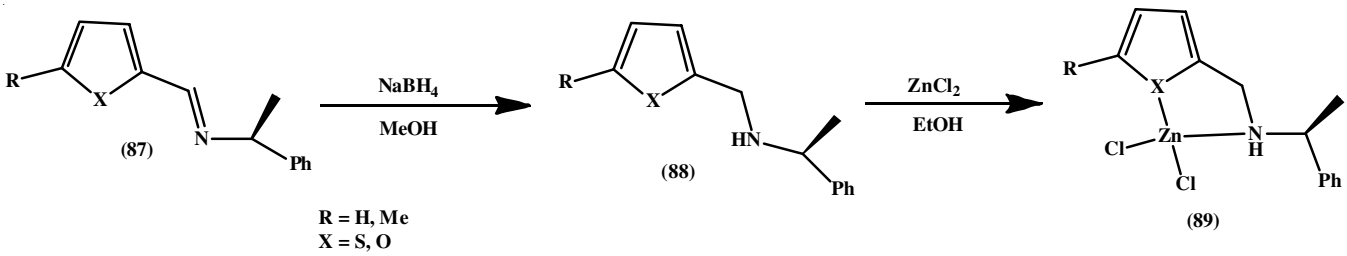
Scheme-XVI: Synthesis of copper(II) and zinc(II) complexes with hydrazide ligands



Scheme-XVII: Synthesis of Schiff base ligand (HL′)



Scheme-XVIII: Synthesis of azido-bridged copper(II) complex



Scheme-XIX: Synthesis of zinc complexes containing thiophenyl and furyl based chiral amines

The reaction between Schiff base 4-chloro-2-((pyridine-2-ylmethylene)phenol derived from 2-pyridinecarboxaldehyde and 2-amino-4-chlorophenyl and $CuCl_2$ afforded (4-chloro-2-((pyridine-2-ylmethylene)amino)phenolato)copper(II) complex (**90**) (Fig. 18) as reported by Ji *et al.* [151]. Copper(II) complexes were found to be strongly inhibit jack bean urease compared to the reference drug acetohydroxamic acid. Molecular docking studies showed that Schiff base containing electron withdrawing groups increase their biological activity.

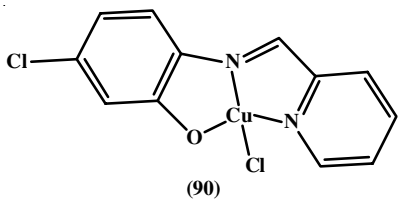


Fig. 18. Copper complex derived from Schiff base 4-chloro-2-((pyridine-2-ylmethylene)phenol

Conclusion

The inhibition of the urease enzyme stands as a pivotal factor in the treatment of gastrointestinal and urinary ailments, prompting extensive research within the scientific community. The involvement of Schiff bases and their metal complexes in this inhibition process garners significant interest due to their crucial role. Numerous studies underscore the importance of Schiff base metal complexes in this context. Within this review, a concise overview of the urease inhibitory properties exhibited by Schiff bases and their metal complexes. This review aims to motivate researchers to develop economically feasible and environmentally friendly Schiff-based metal complexes that inhibit the urease enzyme.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. A.D. Larson and R.E. Kallio, *J. Bacteriol.*, **68**, 67 (1954); https://doi.org/10.1128/jb.68.1.67-73.1954
2. B.S. Senthil, F. Fazila and S. Jayalakshmi, *Afr. J. Microbiol. Res.*, **6**, 5914 (2012).
3. F. Mirbod, R.A. Schaller and G.T. Cole, *Med. Mycol.*, **40**, 35 (2002); https://doi.org/10.1080/mmy.40.1.35.44
4. I.T. Bekheet and P.J. Syrett, *J. Phycol.*, **12**, 137 (1977); https://doi.org/10.1080/00071617700650151
5. P.A. Karplus, M.A. Pearson and R.P. Hausinger, *Acc. Chem. Res.*, **30**, 330 (1997); https://doi.org/10.1021/ar960022j
6. R.H. Holm, P. Kennepohl and E.I. Solomon, *Chem. Rev.*, **96**, 2239 (1996); https://doi.org/10.1021/cr9500390
7. C.M. Reynolds, D.C. Wolf and J.A. Armbruster, *Soil Sci. Soc. Am. J.*, **49**, 104 (1985); https://doi.org/10.2136/sssaj1985.03615995004900010021x

8. R.S. Dharmakeerthi and M.W. Thenabadu, *J. Natn. Sci. Coun. Sri Lanka*, **24**, 159 (1996).
9. Q. Zhengping, O.V. Cleemput, P. Demeyer and L. Baert, *Biol. Fertil. Soils*, **11**, 43 (1991); https://doi.org/10.1007/BF00335833
10. H.L. Mobley and R.P. Hausinger, *Microbiol. Rev.*, **53**, 85 (1989); https://doi.org/10.1128/mr.53.1.85-108.1989
11. K.L. Sahrawat, *Plant Soil*, **57**, 335 (1980); https://doi.org/10.1007/BF02211691
12. R.L. Mulvaney and J.M. Bremner, Eds.: E.A. Paul and J.N. Ladd, Control of Urea Transformations in Soils, In: Soil biochemistry, Marcel Dekker, New York, vol. 5, pp 153-196 (1981).
13. A. Zimber and W.J. Visek, *Am. J. Physiol.*, **223**, 1004 (1972); https://doi.org/10.1152/ajplegacy.1972.223.4.1004
14. Z.M. Huang, Y.Y. Qi, S.H. Du, G. Feng, H. Unuma and W.Q. Yan, *Sci. Technol. Adv. Mater.*, **14**, 055001 (2013); https://doi.org/10.1088/1468-6996/14/5/055001
15. H.L. Mobley, M.D. Island and R.P. Hausinger, *Microbiol. Rev.*, **59**, 451 (1995); https://doi.org/10.1128/mr.59.3.451-480.1995
16. D.P. Griffith, *Kidney Int.*, **13**, 372 (1978); https://doi.org/10.1038/ki.1978.55
17. R.K. Andrews, A. Dexter, R.L. Blakeley and B. Zerner, *J. Am. Chem. Soc.*, **108**, 7124 (1986); https://doi.org/10.1021/ja00282a059
18. L.E. Zonia, N.E. Stebbins and J.C. Polacco, *Plant Physiol.*, **107**, 1097 (1995); https://doi.org/10.1104/pp.107.4.1097
19. G. Estiu and K.M. Merz, *J. Am. Chem. Soc.*, **126**, 6932 (2004); https://doi.org/10.1021/ja049327g
20. G. Estiu and K.M. Merz, *Biochemistry*, **45**, 4429 (2006); https://doi.org/10.1021/bi052020p
21. T. Aoyagi, G.W. Engstrom, W.B. Evans and W.H. Summerskill, *Gut*, **7**, 631 (1966); https://doi.org/10.1136/gut.7.6.631
22. G.H. Carpenter, *J. Dent. Res.*, **99**, 644 (2020); https://doi.org/10.1177/0022034520915486
23. R.J.C. McLean, J.C. Nickel, K.-J. Cheng, J.W. Costerton and J.G. Banwell, *CRC Crit. Rev. Microbiol.*, **16**, 37 (1988); https://doi.org/10.3109/10408418809104467
24. I. Konieczna, P. Zarnowiec, M. Kwinkowski, B. Kolesinska, J. Fraczyk, Z. Kaminski and W. Kaca, *Curr. Protein Pept. Sci.*, **13**, 789 (2012); https://doi.org/10.2174/138920312804871094
25. C. Follmer, *J. Clin. Pathol.*, **63**, 424 (2010); https://doi.org/10.1136/jcp.2009.072595
26. H.M. Shihab and A.M.N. Khaleel, *Chem. Methodol.*, **7**, 137 (2023); https://doi.org/10.22034/chemm.2023.363773.1613
27. I.J. Rosenstein, J.M. Hamilton-Miller and W. Brumfitt, *Infect. Immun.*, **32**, 32 (1981); https://doi.org/10.1128/iai.32.1.32-37.1981
28. D.M. Musher, D.P. Griffith, D. Yawn and R.D. Rossen, *J. Infect. Dis.*, **131**, 177 (1975); https://doi.org/10.1093/infdis/131.2.177
29. M.J. Maroney and S. Ciurli, *Chem. Rev.*, **114**, 4206 (2014); https://doi.org/10.1021/cr4004488
30. J.L. Boer, S.B. Mulrooney and R.P. Hausinger, *Arch. Biochem. Biophys.*, **544**, 142 (2014); https://doi.org/10.1016/j.abb.2013.09.002
31. B. Krajewska, *J. Mol. Catal. B Enzym.*, **59**, 9 (2009); https://doi.org/10.1016/j.molcatb.2009.01.003
32. Zaheer-ul-Haq, M.A. Lodhi, S.A. Nawaz, S. Iqbal, K.M. Khan, B.M. Rode, Atta-ur-Rahman and M.I. Choudhary, *Bioorg. Med. Chem.*, **16**, 3456 (2008); https://doi.org/10.1016/j.bmc.2005.09.048
33. S. Schindler, *Eur. J. Inorg. Chem.*, **2000**, 2311 (2000); https://doi.org/10.1002/1099-0682(200011)2000:11<2311::AID-EJIC2311>3.0.CO;2-7
34. K. Shahzadi, S.M. Bukhari, A. Zaidi, T.A. Wani, M.S. Jan, S. Zargar, U. Rashid, U. Farooq, A. Khushal and S. Khan, *Pharmaceuticals*, **16**, 1552 (2023); https://doi.org/10.3390/ph16111552
35. Y. Onoda, H. Iwasaki, T. Magaribuchi and H. Tamaki, *Arzneimittelforschung*, **41**, 546 (1991).
36. G.W. McCarty, J.M. Bremner and J.S. Lee, *Plant Soil*, **127**, 269 (1990); https://doi.org/10.1007/BF00014435
37. Y.N. Wang, S.Y. Li, L.C. Yuan, S.F. Bu, Y. Zeng, Z.P. Xiao and H.L. Zhu, *Bioorg. Med. Chem.*, **102**, 117656 (2024); https://doi.org/10.1016/j.bmc.2024.117656
38. C.S. Dohanik, C.P. Pereira, B.G. de Oliveira, I.J. Nascimento, A.L.A. Nascimento, J.C. Santos, T.M. de Aquino, R.O. Castilho, L.V. Modolo, A.D. Fatima and G.A. Goulart, *J. Braz. Chem. Soc.*, **35**, e-20240001 (2024); https://doi.org/10.21577/0103-5053.20240001
39. K.B. Kc, G.M. Dias, A. Veeramani, C.J. Swanton, D. Fraser, D. Steinke, E. Lee, H. Wittman, J.M. Farber, K. Dunfield, K. McCann, M. Anand, M. Campbell, N. Rooney, N.E. Raine, R.V. Acker, R. Hanner, S. Pascoal, S. Sharif, T.G. Benton and E.D.G. Fraser, *PLoS One*, **13**, e0205683 (2018); https://doi.org/10.1371/journal.pone.0205683
40. N. Dharmaraj, P. Viswanathamurthi and K. Natarajan, *Transition Met. Chem.*, **26**, 105 (2001); https://doi.org/10.1023/A:1007132408648
41. J. Saranya, S. Jone Kirubavathy, S. Chitra, A. Zarrouk, K. Kalpana, K. Lavanya and B. Ravikiran, *Arab. J. Sci. Eng.*, **45**, 4683 (2020); https://doi.org/10.1007/s13369-020-04416-7
42. G. Matela, *Anticancer. Agents Med. Chem.*, **20**, 1908 (2020); https://doi.org/10.2174/1871520620666200507091207
43. Q.-U.-A. Sandhu, M. Pervaiz, A. Majid, U. Younas, Z. Saeed, A. Ashraf, R.R.M. Khan, S. Ullah, F. Ali and S. Jelani, *J. Coord. Chem.*, **76**, 1094 (2023); https://doi.org/10.1080/00958972.2023.2226794
44. A. Avila-Sorrosa, A.Y. Bando-Vázquez, V. Alvarez-Alvarez, E. Suarez-Contreras, R. Nieto-Meneses, B. Nogueda-Torres, M.E. Vargas-Díaz, F. Díaz-Cedillo, R. Reyes-Martínez, S. Hernandez-Ortega and D. Morales-Morales, *J. Mol. Struct.*, **1218**, 128520 (2020); https://doi.org/10.1016/j.molstruc.2020.128520
45. N.A. Al-Masoudi, N.M. Aziz and A.T. Mohammed, *Phosphorus Sulfur Silicon Rel. Elem.*, **184**, 2891 (2009); https://doi.org/10.1080/10426500802591630
46. K. Meena and P.K. Baroliya, *Chem. Biodivers.*, **20**, e202300158 (2023); https://doi.org/10.1002/cbdv.202300158
47. D.P. Griffith, *Kidney Int.*, **13**, 372 (1978); https://doi.org/10.1038/ki.1978.55
48. D.-H. Shi, Z.-L. You, C. Xu, Q. Zhang and H.-L. Zhu, *Inorg. Chem. Commun.*, **10**, 404 (2007); https://doi.org/10.1016/j.inoche.2006.12.011
49. C. Boulechfar, H. Ferkous, A. Delimi, A. Djedouani, A. Kahlouche, A. Boublia, A.S. Darwish, T. Lemaoui, R. Verma and Y. Benguerba, *Inorg. Chem. Commun.*, **150**, 110451 (2023); https://doi.org/10.1016/j.inoche.2023.110451
50. E. Wolpert, A.F. Hofmann and W.H.J. Summerskill, *Exp. Biol. Med.*, **136**, 592 (1971); https://doi.org/10.3181/00379727-136-35318
51. X. Liu, M. Zhang, Z. Li, C. Zhang, C. Wan, Y. Zhang and D.-J. Lee, *Bioresour. Technol.*, **290**, 121767 (2019); https://doi.org/10.1016/j.biortech.2019.121767
52. Z. Amtul, B.S.P. Atta-ur-Rahman, R. Siddiqui and M. Choudhary, *Curr. Med. Chem.*, **9**, 1323 (2002); https://doi.org/10.2174/0929867023369853
53. W. Zaborska, M. Kot and K. Superata, *J. Enzyme Inhib. Med. Chem.*, **17**, 247 (2002); https://doi.org/10.1080/14756360210000011670
54. T. Tanaka, M. Kawase and S. Tani, *Bioorg. Med. Chem.*, **12**, 501 (2004); https://doi.org/10.1016/j.bmc.2003.10.017
55. W. Zaborska, B. Krajewska and Z. Olech, *J. Enzyme Inhib. Med. Chem.*, **19**, 65 (2004); https://doi.org/10.1080/14756360310001650237
56. W. Zaborska, B. Krajewska, M. Leszko and Z. Olech, *J. Mol. Catal., B Enzym.*, **13**, 103 (2001); https://doi.org/10.1016/S1381-1177(00)00234-4
57. X. Dong, Y. Li, Z. Li, Y. Cui and H. Zhu, *J. Inorg. Biochem.*, **108**, 22 (2012); https://doi.org/10.1016/j.jinorgbio.2011.12.006

58. K. Cheng, Q.-Z. Zheng and H.-L. Zhu, *Inorg. Chem. Commun.*, **12**, 1116 (2009); https://doi.org/10.1016/j.inoche.2009.09.001
59. Z.-L. You, L. Zhang, D.-H. Shi, X.-L. Wang, X.-F. Li and Y.-P. Ma, *Inorg. Chem. Commun.*, **13**, 996 (2010); https://doi.org/10.1016/j.inoche.2010.05.016
60. X. Qiu, J. Wang, D. Shi, S. Li, F. Zhang, F. Zhang, G. Cao and B. Zhai, *J. Coord. Chem.*, **66**, 1616 (2013); https://doi.org/10.1080/00958972.2013.787144
61. R. Ara, U. Ashiq, M. Mahroof-Tahir, Z.T. Maqsood, K.M. Khan, M.A. Lodhi and M.I. Choudhary, *Chem. Biodivers.*, **4**, 58 (2007); https://doi.org/10.1002/cbdv.200790007
62. S. Benini, W.R. Rypniewski, K.S. Wilson, S. Mangani and S. Ciurli, *J. Am. Chem. Soc.*, **126**, 3714 (2004); https://doi.org/10.1021/ja049618p
63. M.J. Todd and R.P. Hausinger, *Biochemistry*, **39**, 5389 (2000); https://doi.org/10.1021/bi992287m
64. K. Kobashi, J. Hase and K. Uehara, *Biochim. Biophys. Acta*, **65**, 380 (1962); https://doi.org/10.1016/0006-3002(62)91067-3
65. E.M.F. Muri, H. Mishra, M.A. Avery and J.S. Williamson, *Synth. Commun.*, **33**, 1977 (2003); https://doi.org/10.1081/SCC-120021024
66. M. Kot, W. Zaborska and K. Orlinska, *J. Enzyme Inhib.*, **16**, 507 (2001); https://doi.org/10.1080/14756360127569
67. S. Matsubara, H. Shibata, F. Ishikawa, T. Yokokura, M. Takahashi, T. Sugimura and K. Wakabayashi, *Biochem. Biophys. Res. Commun.*, **310**, 715 (2003); https://doi.org/10.1016/j.bbrc.2003.09.066
68. J.-E. Shin, J.-M. Kim, E.-A. Bae, Y.-J. Hyun and D.-H. Kim, *Planta Med.*, **71**, 197 (2005); https://doi.org/10.1055/s-2005-837816
69. Z. Amtul, M. Rasheed, M.I. Choudhary, S. Rosanna, K.M. Khan and Atta-ur-Rahman, *Biochem. Biophys. Res. Commun.*, **319**, 1053 (2004); https://doi.org/10.1016/j.bbrc.2004.05.036
70. S. Ciurli, S. Benini, W.R. Rypniewski, K.S. Wilson, S. Miletti and S. Mangani, *Coord. Chem. Rev.*, **190-192**, 331 (1999); https://doi.org/10.1016/S0010-8545(99)00093-4
71. M. Biglar, K. Soltani, F. Nabati, R. Bazl, F. Mojab and M. Amanlou, *Iran. J. Pharm. Res.*, **11**, 831 (2012).
72. S. Vassiliou, P. Kosikowska, A. Grabowiecka, A. Yiotakis, P. Kafarski and L. Berlicki, *J. Med. Chem.*, **53**, 5597 (2010); https://doi.org/10.1021/jm100340m.
73. S. Benini, M. Cianci, L. Mazzei and S. Ciurli, *J. Biol. Inorg. Chem.*, **19**, 1243 (2014); https://doi.org/10.1007/s00775-014-1182-x
74. W. Chen, Y. Li, Y. Cui, X. Zhang, H.-L. Zhu and Q. Zeng, *Eur. J. Med. Chem.*, **45**, 4473 (2010); https://doi.org/10.1016/j.ejmech.2010.07.007
75. T.T. Tidwell, *Angew. Chem. Int. Ed.*, **47**, 1016 (2008); https://doi.org/10.1002/anie.200702965
76. A. Kajal, S. Bala, S. Kamboj, N. Sharma and V. Saini, *J. Cat.*, **2013**, 893512 (2013); https://doi.org/10.1155/2013/893512
77. S. Arulmurugan, H. P. Kavitha, B. R. Venkatraman, *Rasayan J. Chem.*, **3**, 385 (2010).
78. N.K. Chaudhary, B. Guragain, S.K. Chaudhary and P. Mishra, *Bibechana*, **18**, 214 (2021); https://doi.org/10.3126/bibechana.v18i1.29841
79. V. Pawariya, S. De and J. Dutta, *Carbohydr. Polym.*, **323**, 121395 (2023); https://doi.org/10.1016/j.carbpol.2023.121395
80. S.A. Dalia, F. Afsan, M.S. Hossain, M.N. Khan, C. Zakaria, M.E. Zahan and M. Ali, *Int. J. Chem. Stud.*, **6**, 2859 (2018).
81. P.G. Cozzi, *Chem. Soc. Rev.*, **33**, 410 (2004); https://doi.org/10.1039/B307853C
82. P.A. Vigato and S. Tamburini, *Coord. Chem. Rev.*, **248**, 1717 (2004); https://doi.org/10.1016/j.cct.2003.09.003
83. W.C. Hung and C.C. Lin, *Inorg. Chem.*, **48**, 728 (2009); https://doi.org/10.1021/ic801397t
84. P. Wu, D.K. Ma, C.H. Leung, S.C. Yan, N. Zhu, R. Abagyan and C.M. Che, *Chem. Eur. J.*, **15**, 13008 (2009); https://doi.org/10.1002/chem.200901943
85. J.F.M. Silva, S.J. Garden and A.C. Pinto, *J. Braz. Chem. Soc.*, **12**, 273 (2001); https://doi.org/10.1590/S0103-50532001000300002
86. J.S. Casas, M.V. Castano, M.C. Cifuentes, A. Sanchez and J. Sordo, *Polyhedron*, **21**, 1651 (2002); https://doi.org/10.1016/S0277-5387(02)01035-5
87. S.N. Pandeya, S. Smitha, M. Jyoti and S.K. Sridhar, *Acta Pharm.*, **55**, 27 (2005).
88. M.M. Sephora Master's thesis, Isolation of Antiplasmodial Naphthyl-isoquinoline Alkaloids from *Ancistrocladus* sp. through Bioassay Guided Fractionation, University of Pretoria, South Africa (2019).
89. K. K. Abubakar, Ph.D. Thesis, Synthesis, Characterization and Applications of Schiff Base Transition Metal Complexes Derived from Salicylaldehyde with 2-Aminophenol and *o*-Phenylenediamine, Kwara State University, Nigeria (2022).
90. R. Fontana, P.C.R. Marconi, A. Caputo and V.B. Gavalyan, *Molecules*, **27**, 2740 (2022); https://doi.org/10.3390/molecules27092740
11. M.A.S. Aslam, S. Mahmood, M. Shahid, A. Saeed and J. Iqbal, *Eur. J. Med. Chem.*, **46**, 5473 (2011); https://doi.org/10.1016/j.ejmech.2011.09.009
92. M.I. Choudhary, A. Khan, K.M. Khan, N. Ambreen, A.T. Wahab and A.U. Rahman, US Patent US20150368214A1 (2015).
93. A. Saeed, A. Imran, P. A. Channar, M. Shahid, W. Mahmood and J. Iqbal, *Chem. Biol. Drug Des.*, **85**, 225 (2014); https://doi.org/10.1111/cbdd.12379
94. C. Vilanova, S. Torijano-Gutiérrez, S. Díaz-Oltra, J. Murga, E. Falomir, M. Carda and J. Alberto Marco, *Eur. J. Med. Chem.*, **87**, 125 (2014); https://doi.org/10.1016/j.ejmech.2014.09.053
95. L.-Y. Ma, L.-P. Pang, B. Wang, M. Zhang, B. Hu, D.-Q. Xue, K.-P. Shao, B.-L. Zhang, Y. Liu, E. Zhang and H.-M. Liu, *Eur. J. Med. Chem.*, **86**, 368 (2014); https://doi.org/10.1016/j.ejmech.2014.08.010
96. G.E.-D.A.A. Abuo-Rahma, M. Abdel-Aziz, N.A. Farag and T.S. Kaoud, *Eur. J. Med. Chem.*, **83**, 398 (2014); https://doi.org/10.1016/j.ejmech.2014.06.049
97. K. Mohan Krishna, B. Inturi, G.V. Pujar, M.N. Purohit and G.S. Vijaykumar, *Eur. J. Med. Chem.*, **84**, 516 (2014); https://doi.org/10.1016/j.ejmech.2014.07.051
98. K. Kumar, B. Pradines, M. Madamet, R. Amalvict and V. Kumar, *Eur. J. Med. Chem.*, **86**, 801 (2014); https://doi.org/10.1016/j.ejmech.2014.10.024
99. A.T. Mavrova, D. Wesselinova, J.A. Tsenov and L.A. Lubenov, *Eur. J. Med. Chem.*, **86**, 676 (2014); https://doi.org/10.1016/j.ejmech.2014.09.032
100. R. Romagnoli, P.G. Baraldi, M.K. Salvador, F. Prencipe, V. Bertolasi, M. Cancellieri, A. Brancale, E. Hamel, I. Castagliuolo, F. Consolaro, E. Porcù, G. Basso and G. Viola, *J. Med. Chem.*, **57**, 6795 (2014); https://doi.org/10.1021/jm5008193
101. T. Plech, B. Kapron, J.J. Luszczki, A. Paneth, M. Kolaczkowski, A. Siwek, M. Zolnierek and G. Nowak, *Eur. J. Med. Chem.*, **86**, 690 (2014); https://doi.org/10.1016/j.ejmech.2014.09.034
102. Y.-P. Xu, J. Qin, S.-M. Sun, T.-T. Liu, X.-L. Zhang, S.-S. Qian and H.-L. Zhu, *Inorg. Chim. Acta*, **423**, 469 (2014); https://doi.org/10.1016/j.ica.2014.09.012
103. P. Elías-Rodríguez, E. Moreno-Clavijo, A.T. Carmona, A.J. Moreno-Vargas and I. Robina, *Org. Biomol. Chem.*, **12**, 5898 (2014); https://doi.org/10.1039/C4OB00931B
104. M. Rafiq, M. Saleem, F. Jabeen, M. Hanif, S.-Y. Seo, S.K. Kang and K.H. Lee, *J. Mol. Struct.*, **1138**, 177 (2017); https://doi.org/10.1016/j.molstruc.2017.03.013
105. H. Aman, N. Rashid, Z. Ashraf, A. Bibi, H.T. Chen and N. Sathishkumar, *Heliyon*, **6**, e05187 (2019); https://doi.org/10.1016/j.heliyon.2020.e05187
106. A. Hamad, M. Abbas Khan, I. Ahmad, A. Imran, R. Khalil, T. Al-Adhami, K. Miraz Rahman, Quratulain, N. Zahra and Z. Shafiq, *Bioorg. Chem.*, **105**, 104336 (2020); https://doi.org/10.1016/j.bioorg.2020.104336

107. H. Štorkánová, S. Oreská, M. Špiritoviæ, B. Heømánková, K. Bubová, M. Komarc, K. Pavelka, J. Vencovský, J.H.W. Distler, L. Šenolt, R. Beèváø and M. Tomèík, *Sci. Rep.*, **11**, 1 (2021); https://doi.org/10.1038/s41598-020-79139-8
108. M.S. Noori, J.D. O'Brien, Z.J. Champa, S.P. Deosarkar, O.L. Lanier, C. Qi, M.M. Burdick, F.L. Schwartz, S.C. Bergmeier, K.D. McCall and D.J. Goetz, *Eur. J. Pharmacol.*, **803**, 130 (2017); https://doi.org/10.1016/j.ejphar.2017.03.049
109. S.M. Gomha, T.T. El-Idreesy, B.K.A. Mabrouk and A.R. Sayed, *Synth. Commun.*, **47**, 2232 (2017); https://doi.org/10.1080/00397911.2017.1370113
110. T. Aziz, A. Ullah, R. Ullah, F. Haq, M. Iqbal, F.U. Khan and M. Kiran, *Biomed. J. Sci. Tech. Res.*, **30**, 23615 (2020); https://doi.org/10.26717/BJSTR.2020.30.004991
111. P. Krishnamoorthy, P. Sathyadevi, P.T. Muthiah and N. Dharmaraj, *RSC Adv.*, **2**, 12190 (2012); https://doi.org/10.1039/c2ra20597a
112. B. Rosenberg, L. Vancamp, J.E. Trosko and V.H. Mansour, *Nature*, **222**, 385 (1996); https://doi.org/10.1038/222385a0
113. C. Jing, C. Wang, K. Yan, K. Zhao, G. Sheng, D. Qu, F. Niu, H. Zhu and Z. You, *Bioorg. Med. Chem.*, **24**, 270 (2016); https://doi.org/10.1016/j.bmc.2015.12.013
114. Z.-L. You, H.-L. Zhu and W.-S. Liu, *J. Inorg. Gen. Chem.*, **630**, 1617 (2004); https://doi.org/10.1002/zaac.200400125
115. Y.-G. Li, D.-H. Shi, H.-L. Zhu, H. Yan and S.W. Ng, *Inorg. Chim. Acta*, **360**, 2881 (2007); https://doi.org/10.1016/j.ica.2007.02.019
116. W. Chen, Y. Li, Y. Cui, X. Zhang, H.-L. Zhu and Q. Zeng, *Eur. J. Med. Chem.*, **45**, 4473 (2010); https://doi.org/10.1016/j.ejmech.2010.07.007
117. J.F.M. Silva, S.J. Garden and A.C. Pinto, *J. Braz. Chem. Soc.*, **12**, 273 (2001); https://doi.org/10.1590/S0103-50532001000300002
118. S.N. Pandeya, S. Smitha, M. Jyoti and S.K. Sridhar, *Acta Pharm.*, **55**, 27 (2005).
119. H. Pervez, M.S. Iqbal, M. Y. Tahir, F.H. Nasim, M.I. Chodhary and K.M. Khan, *J. Enzyme Inhib. Med. Chem.*, **23**, 848 (2007); https://doi.org/10.1080/14756360701746179
120. R. Ara, U. Ashiq, M. Mahroof-Tahir, Z.T. Maqsood, K.M. Khan, M.A. Lodhi and M.I. Choudhary, *Chem. Biodivers.*, **4**, 58 (2007); https://doi.org/10.1002/cbdv.200790007
121. Z.-L. You and P. Zhou, *Inorg. Chem. Commun.*, **10**, 1273 (2007); https://doi.org/10.1016/j.inoche.2007.08.007
122. C.-Y. Wang, X. Wu, S.-J. Tu and B. Jiang, *Synth. React. Inorg. Met.-Org. Nano-Met. Chem.*, **39**, 78 (2009); https://doi.org/10.1080/15533170902762603
123. C.P. Raptopoulou, A.N. Papadopoulos, D.A. Malamatari, E. Ioannidis, G. Moisidis, A. Terzis and D.P. Kessissoglou, *Inorg. Chim. Acta*, **272**, 283 (1998); https://doi.org/10.1016/S0020-1693(97)05876-3
124. Z.-L. You, P. Hou, L.-L. Ni and S. Chen, *Inorg. Chem. Commun.*, **12**, 444 (2009); https://doi.org/10.1016/j.inoche.2009.03.009
125. Z.-L. You, Y. Lu, N. Zhang, B.-W. Ding, H. Sun, P. Hou and C. Wang, *Polyhedron*, **30**, 2186 (2011); https://doi.org/10.1016/j.poly.2011.05.048
126. C. Jing, C. Wang, K. Yan, K. Zhao, G. Sheng, D. Qu, F. Niu, H. Zhu and Z. You, *Bioorg. Med. Chem.*, **24**, 270 (2016); https://doi.org/10.1016/j.bmc.2015.12.013
127. L. Pan, C. Wang, K. Yan, K. Zhao, G. Sheng, H. Zhu, X. Zhao, D. Qu, F. Niu and Z. You, *J. Inorg. Biochem.*, **159**, 22 (2016); https://doi.org/10.1016/j.jinorgbio.2016.02.017
128. M.K. Rauf, S. Yaseen, A. Badshah, S. Zaib, R. Arshad, Imtiaz-ud-Din, M.N. Tahir and J. Iqbal, *J. Biol. Inorg. Chem.*, **20**, 541 (2015); https://doi.org/10.1007/s00775-015-1239-5
129. M. Jamil, N. Sultana, M. Sarfraz, M.N. Tahir and M.I. Tariq, *Iran. J. Chem. Chem. Eng.*, **39**, 45 (2020).
130. W. Radecka-Paryzek, I. Pospieszna-Markiewicz and M. Kubicki, *Inorg. Chim. Acta*, **360**, 488 (2007); https://doi.org/10.1016/j.ica.2006.07.071
131. C.M. Collins and S.E.F. D'Orazio, *Mol. Microbiol.*, **9**, 907 (1993); https://doi.org/10.1111/j.1365-2958.1993.tb01220.x
132. Y. Cui, X. Dong, Y. Li, Z. Li and W. Chen, *Eur. J. Med. Chem.*, **58**, 323 (2012); https://doi.org/10.1016/j.ejmech.2012.09.037
133. Y. Lu, D.-H. Shi, Z.-L. You, X.-S. Zhou and K. Li, *J. Coord. Chem.*, **65**, 339 (2012); https://doi.org/10.1080/00958972.2011.653785
134. A.N. Kharat, A. Bakhoda, G. Bruno and H.A. Rudbari, *Polyhedron*, **45**, 9 (2012); https://doi.org/10.1016/j.poly.2012.07.035
135. X. Qiu, J. Wang, D. Shi, S. Li, F. Zhang, F. Zhang, G. Cao and B. Zhai, *J. Coord. Chem.*, **66**, 1616 (2013); https://doi.org/10.1080/00958972.2013.787144
136. Y. Li, Z. Li, Y. Liu, X. Dong and Y. Cui, *J. Coord. Chem.*, **65**, 19 (2012); https://doi.org/10.1080/00958972.2011.637169
137. Y. Li, H. Jing, C. Ma and Q. Wang, *Transition Met. Chem.*, **40**, 743 (2015); https://doi.org/10.1007/s11243-015-9969-3
138. M. Ikram, S. Rehman, Faridoon, R.J. Baker, H.U. Rehman, A. Khan, M.I. Choudhary and S.-U. -Rehman, *Thermochim. Acta*, **555**, 72 (2013); https://doi.org/10.1016/j.tca.2012.12.023
139. Y. Gou, M. Yu, Y. Li, Y. Peng and W. Chen, *Inorg. Chim. Acta*, **404**, 224 (2013); https://doi.org/10.1016/j.ica.2013.03.045
140. Y.P. Xu, Y.H. Chen, Z.J. Chen, J. Qin, S.S. Qian, H.L. Zhu, *Eur. J. Inorg. Chem.*, **2015**, 2076 (2015); https://doi.org/10.1002/ejic.201500050
141. S. Sangeeta, K. Ahmad, N. Noorussabah, S. Bharti, M.K. Mishra, S.R. Sharma and M. Choudhary, *J. Mol. Struct.*, **1156**, 1 (2018); https://doi.org/10.1016/j.molstruc.2017.11.062
142. Y. Li, H. Jing, C. Ma and Q. Wang, *Transition Met. Chem.*, **40**, 743 (2015); https://doi.org/10.1007/s11243-015-9969-3
143. H. Pervez, M. Ahmad, S. Zaib, M. Yaqub, M.M. Naseer and J. Iqbal, *MedChemComm*, **7**, 914 (2016); https://doi.org/10.1039/C5MD00529A
144. Z. Zong, X. Wei, X. Yan and Y. Fan, *J. Mol. Struct.*, **1171**, 333 (2018); https://doi.org/10.1016/j.molstruc.2018.06.019
145. Y.L. Wang, X. Zhang, X.M. Meng, X. Li, C.F. Bi and Y.H. Fan, *Transition Met. Chem.*, **41**, 897 (2016); https://doi.org/10.1007/s11243-016-0092-x
146. M. Duan, Y. Li, L. Xu, H. Yang, F. Luo, Y. Guan, B. Zhang, C. Jing and Z. You, *Inorg. Chem. Commun.*, **100**, 27 (2019); https://doi.org/10.1016/j.inoche.2018.12.009
147. M. Hanif, F. Kanwal, M. Rafiq, M. Hassan, M. Mustaqeem, S.-Y. Seo, Y. Zhang, C. Lu, T. Chen and M. Saleem, *Molecules*, **24**, 312 (2019); https://doi.org/10.3390/molecules24020312
148. F.-M. Wang, L.-J. Li, G.-W. Zang, T.-T. Deng and Z.-L. You, *Acta Chim. Slov.*, **67**, 1155 (2020); https://doi.org/10.17344/acsi.2020.6056
149. J. Wang, Y. Luo, Y. Zhang, Y. Chen, F. Gao, Y. Ma, D. Xian and Z. You, *J. Coord. Chem.*, **74**, 1028 (2021); https://doi.org/10.1080/00958972.2020.1861603
150. S. Nayab, A. Alam, F.A. Khan, H. Khan, S. Khan and F.A. Khan, *Bull. Chem. Soc. Ethiop.*, **35**, 301 (2021); https://doi.org/10.4314/bcse.v35i2.7
151. J. Ji, S. Wang, J. Zhao, T. Yang, J. Wang and Z. You, *J. Coord. Chem.*, **75**, 120 (2022); https://doi.org/10.1080/00958972.2022.2032005