Review

Schiff bases and their metal complexes as urease inhibitors – A brief review ☆

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GRAPHICAL ABSTRACT

ARTICLE INFO

ABSTRACT

Schiff bases, an aldehyde- or ketone-like compounds in which the carbonyl group is replaced by an imine or azomethine, are some of the most widely used organic compounds. Indeed, they are widely used for industrial purposes and also exhibit a broad range of biological activities, including anti-urease activity. Ureases, enzymes that catalyze urea hydrolysis, have received considerable attention for their impact on living organisms' health, since the persistence of urease activity in human and animal cells can be the cause of some diseases and pathogen infections. This short review compiles examples of the most anti-urease Schiff bases ($0.23\ \mu M < IC_{50} < 37.00\ \mu M$) and their metal complexes ($0.03\ \mu M < IC_{50} < 100\ \mu M$). Emphasis is given to ureases of *Helicobacter pylori* and *Canavalia ensiformis,* although the active site of this class of hydrolases is conserved among living organisms.
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Introduction

Schiff bases are a well-known class of compounds with the general structure $R^1R^2C=NR^3$ (with $R^3 \neq H$) (Fig. 1) [1], and they are named in honor to Hugo Schiff, the scientist who first synthesized members of this class of substances in 1864 [2,3]. Schiff bases are some of the most widely used organic compounds. They serve as pigments and dyes, catalysts, intermediates in organic synthesis, and polymer stabilizers [4,5]. Schiff bases also exhibit a wide variety of biological activities, including antifungal, antibacterial, antitumor, anti-inflammatory, trypanocidal, anti-HIV, antimalarial, and anti-urease activities (reviewed by [1,6–11]). Indeed, the imine group present in these compounds is critical for their biological activities [12], and thus that moiety has been extensively explored for the development of new bioactive substances [13–17].
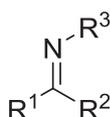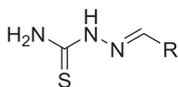
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Urease, a natural enzyme strictly dependent on nickel ions (Ni^{2+}), is widely distributed among plants, fungi and bacteria and belongs to the family of amidohydrolases [18,19]. This type of hydrolase accelerates the rate of urea hydrolysis to ammonia (NH_3) and carbon dioxide (CO_2) one-hundred-trillion-fold [18,20,21]. Increasing the pH of the medium by the generation of NH_3 is a urease trait of tremendous medical importance. For instance, urine and/or gastrointestinal infections by ureolytic bacteria can cause health complications in humans and animals including kidney stone formation, pyelonephritis, hepatic encephalopathy, and ultimately hepatic coma [21,22]. Therefore, there are major public health problems related to *Helicobacter pylori*, which is able to survive in the acid environment of the stomach (pH = 1–2) by excreting urease to the medium and consequently increasing the pH by the accumulation of NH_3, making its microenvironment more favorable for its growth and development [19,23]. Indeed, urease represents 10% of the total protein mass in *H. pylori* [24]. Consequently, *H. pylori* infection can induce gastric inflammation and increase the risk for the development of duodenal and gastric ulcers, gastric adenocarcinoma and gastric lymphoma [3,19]. Urease is also produced by most strains of *Proteus mirabilis* and *Staphylococcus saprophyticus* and by some plasmid-containing strains of *Escherichia coli* [25]. These bacteria are some of the most primary etiological agents related to urinary tract infections, and urease is a key virulence factor that determines the severity of the urinary tract infection [26–28].

Due the tremendous medical importance of ureases, these enzymes have become important therapeutic targets for the treatment of disease caused by urease-dependent pathogenic microorganisms. Here, we present examples of Schiff bases as well as their metal complexes that possesses anti-urease activity, highlighting the most representative compounds/complexes belonging to this class of substances.

R^1, R^2 and/or R^3 = H, alkyl or aryl ($R^3 \neq$ H)

Fig. 1. General structure of Schiff base.

R= (2-Cl)-C_6H_4 (**1**)
R= (3-Cl)-C_6H_4 (**2**)
R= (4-Cl)-C_6H_4 (**3**)
R= (3-Br)-C_6H_4 (**4**)
R= (4-Br)-C_6H_4 (**5**)
R= (3-NO_2)-C_6H_4 (**6**)
R= (4-NO_2)-C_6H_4 (**7**)
R= (3-OCH_3)-C_6H_4 (**8**)
R= (4-OCH_3)-C_6H_4 (**9**)

R= (3,4,5-OCH_3)-C_6H_2 (**10**)
R= (4-N(CH_3)$_2$)-C_6H_4 (**11**)
R= ((E)-CH=CH-C_6H_5)-C_6H_4 (**12**)
R= (2-OCH_2-C_6H_5)-C_6H_4 (**13**)
R= (3-$OCH_2C_6H_5$, 4-OCH_3)-C_6H_3 (**14**)
R= (4-OH)-C_6H_4 (**15**)
R= (2,3-OH)-C_6H_3 (**16**)
R= (4-OH, 3,5-OCH_3)-C_6H_2 (**17**)
R= (E)-CH=$CHCH_3$ (**18**)

Fig. 2. Schiff bases hydrazone derivatives **1–18** synthesized by Aslam and co-workers [29].

Schiff base as urease inhibitors

Although Schiff bases are known to have a variety of biological properties, few examples of this class of substances have been described as potent anti-urease agents. In 2011, Aslam and co-workers described the synthesis and *in vitro* anti-urease activity of 18 Schiff base hydrazone derivatives (Fig. 2). All synthesized compounds exhibited significant urease inhibition, but compound **6** showed the most potent activity (IC_{50} = 0.102 µM) followed by compounds **8** and **11** (IC_{50} = 0.177 and 0.127 µM, respectively). Schiff base hydrazone derivatives **1**, **13**, **14**, **16** and **17** exhibited moderate activity, while analogs **2**, **3**, **4**, **5**, **7**, **9**, **10**, **12**, **15** and **18** showed little effect on urease activity. In general, Schiff base hydrazone derivatives with electron-withdrawing substituents on the aromatic ring showed stronger anti-urease activities than those with electron-donating substituents. Aslam and co-workers also disclosed that compound **6**, which bears an electron-withdrawing group (NO_2) at the *meta* position, exhibited competitively inhibition against urease [29].

In 2014, Saeed and co-workers described the inhibition of purified urease from jack bean by Schiff base thiosemicarbazide derivatives. Out of a series of thirteen compounds, seven of them presented promising abilities to inhibit urease enzyme (Fig. 3; compounds **19–25**). The range of IC_{50} values for Schiff base thiosemicarbazide derivatives **19–25** was 0.58–4.84 µM, and all

R1= (**19**; IC_{50}= 2.65 µM)
R1= (**20**; IC_{50}= 2.41 µM)
R1= (**21**; IC_{50}= 0.58 µM)
R1= (**22**; IC_{50}= 3.23 µM)
R1= (**23**; IC_{50}= 4.24 µM)
R1= (**24**; IC_{50}= 3.64 µM)
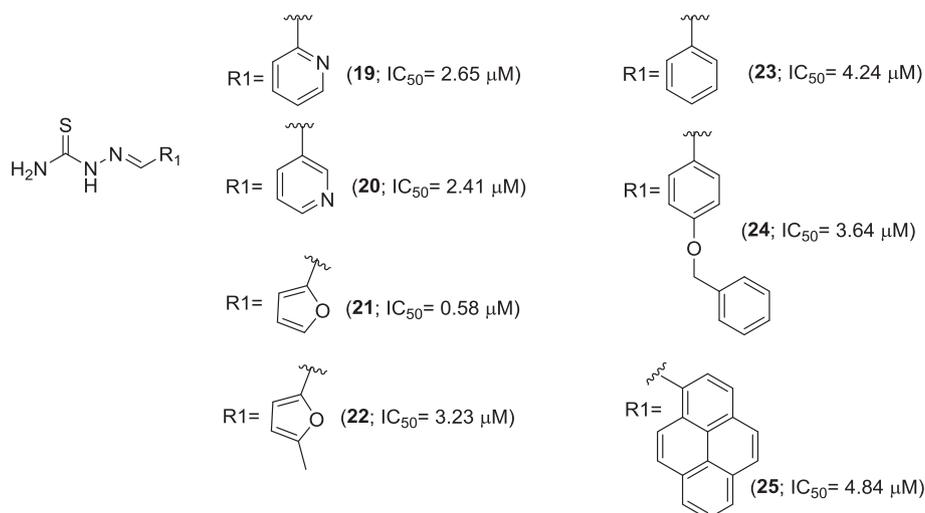R1= (**25**; IC_{50}= 4.84 µM)

Fig. 3. Schiff bases thiosemicarbazide derivatives **18–25** synthesized by Saeed and co-workers [30].
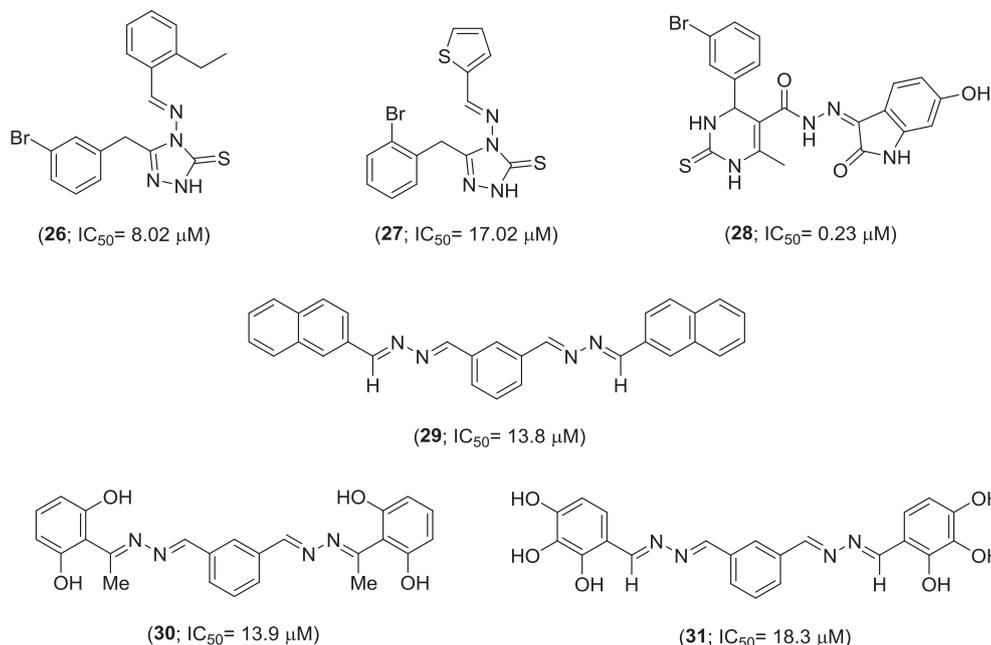
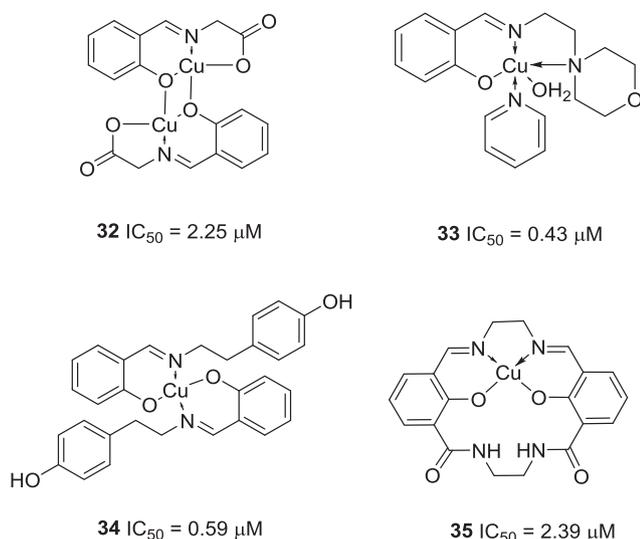Fig. 4. Chemical structures of some Schiff bases 26–31.

Fig. 5. Chemical structures of the first copper complexes reported as urease inhibitors [38,40].

of them were more potent than thiourea (IC_{50} = 21 μM), a positive control used in the urease inhibitory assay [30].

Rafiq and co-workers (2017) reported the preparation of eleven Schiff bases containing 1,2,4-triazole cores and their inhibitory effects on urease activity [31]. Out of this series of Schiff bases, compounds 26 and 27 (Fig. 4) were the most potent with IC_{50} values of 8.02 μM and 17.02 μM, respectively (31)].

Other Schiff bases have also been recognized as potential urease inhibitors. For instance, Iftikhar [32] and co-workers (2017) described dihydropyrimidine (DHPM) 28 as the most potent jack bean urease inhibitor (IC_{50} = 0.23 μM) [32]. Rahim and co-workers showed that bis-Schiff bases 29, 30 and 31 (Fig. 4), derived from isophthalaldehyde, were able to inhibit urease with IC_{50} values of 13.8 μM, 13.9 μM and 18.3 μM, respectively. According to Rahim and co-workers, the urease inhibition by Schiff bases 30 and 31 is due to possible hydrogen bonding between the hydroxyl group present in the Schiff bases and an amino acid residue in the active site of the urease, while the inhibitory effect of 29 might be due to an arene interaction with an amino acid residue [33].
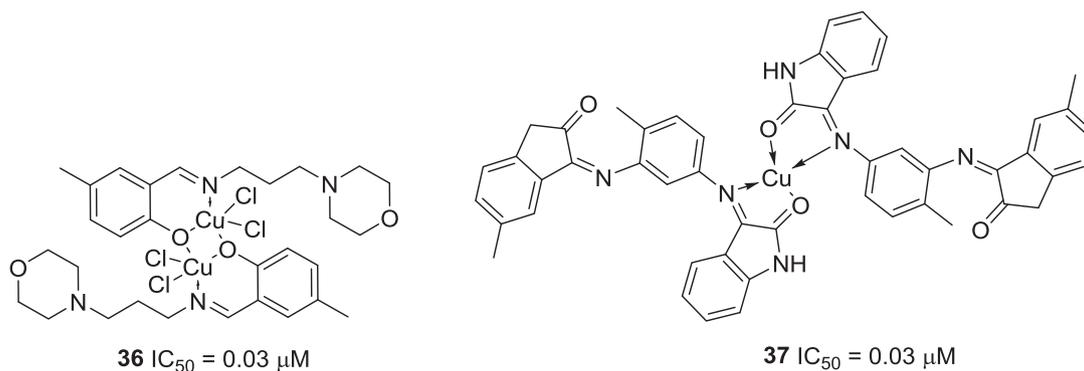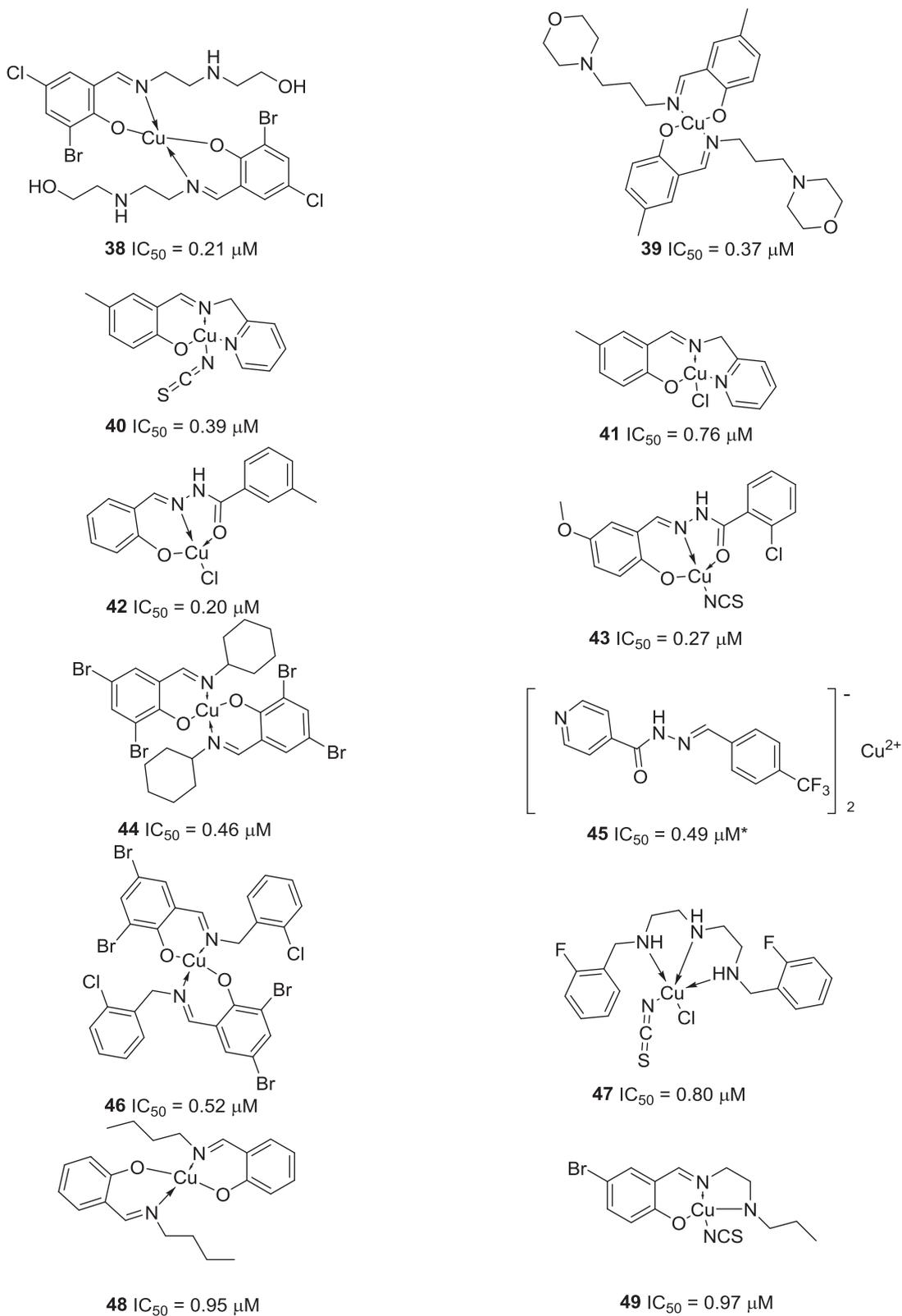

Fig. 6. Chemical structures of some Schiff bases-based Cu complexes 36 and 37 [41,42].

38 IC$_{50}$ = 0.21 μM

39 IC$_{50}$ = 0.37 μM

40 IC$_{50}$ = 0.39 μM

41 IC$_{50}$ = 0.76 μM

42 IC$_{50}$ = 0.20 μM

43 IC$_{50}$ = 0.27 μM

44 IC$_{50}$ = 0.46 μM

45 IC$_{50}$ = 0.49 μM*

46 IC$_{50}$ = 0.52 μM

47 IC$_{50}$ = 0.80 μM

48 IC$_{50}$ = 0.95 μM

49 IC$_{50}$ = 0.97 μM

*There is no X-ray structure for complex 45 to define undoubtedly the coordination geometry. However, data from elemental analysis and infrared spectrum support a metal-ligand ratio of 1:2

Fig. 7. Chemical structures of relevant Schiff bases-based Cu complexes that present IC$_{50}$ values lower than 1.0 μM.
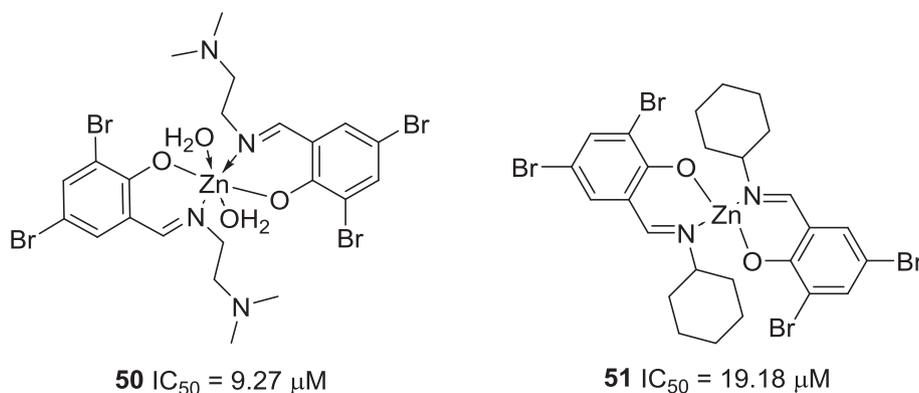
50 IC$_{50}$ = 9.27 µM   **51** IC$_{50}$ = 19.18 µM

Fig. 8. Chemical structures of Cheng's zinc complexes that present high anti-urease activities [44].

52 IC$_{50}$ = 72.19 µM   **53** IC$_{50}$ = 77.36 µM

54 IC$_{50}$ = 72.03 µM   **55** IC$_{50}$ = 86.12 µM
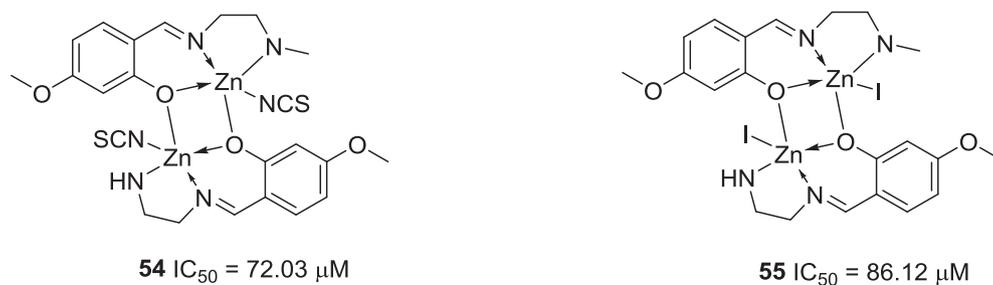
Fig. 9. Chemical structures of zinc complexes synthesized by You's and Wang's research groups [57,58].

Schiff base metal complexes as urease inhibitors

Schiff base copper complexes

Copper is an essential element that is necessary for a wide variety of metabolic processes. A broad range of Cu-containing enzymes are known, and they all serve as redox catalysts or as dioxygen carriers. Copper is classified as a transition metal, and it has three oxidation states: Cu^0, Cu^{1+} and Cu^{2+}. Copper is also classified as a heavy metal since its density is greater than 5 g cm^{-3} [34–36]. Copper (II) (electronic configuration 3d^9), present in most complexes that have urease inhibitory activity, is an ion that exhibits a wide range of stereochemistries, such as tetra-, penta-, and hexa-coordinate geometries [37]. The great interest in copper complexes as urease inhibitors might be due to the strong Lewis acid properties of its metal ions [38]. In a study conducted using jack bean urease enzyme, Follmer and Carlini showed that copper ions can polymerize the protein by modifying it in a way that the enzyme loses its inhibitory activity and through other mechanisms, such as blocking thiol groups in the thiol-dependent

domain, which contains the ureolytic active site, and by binding to histidine residues in the protein [39].

The first copper complexes synthesized and assayed as urease inhibitors were described in 2007 by Zhu's research group (Fig. 5) [38,40]. Zhu and co-workers (2007) synthesized three copper complexes, as well as Ni and Mn complexes, derived from Schiff bases (**32–34**) and evaluated their activities against urease. These authors also tested the free Cu^{2+}, Ni^{2+} and Mn^{2+} ions as inhi-
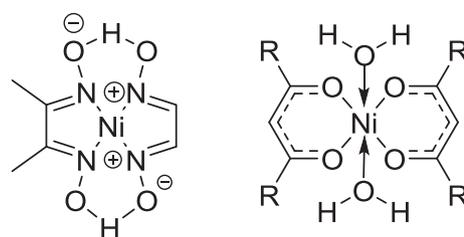

Fig. 10. Nickel (Ni^{2+}) complex with four or six coordinations spheres.

56 IC$_{50}$ = 4.36 μM
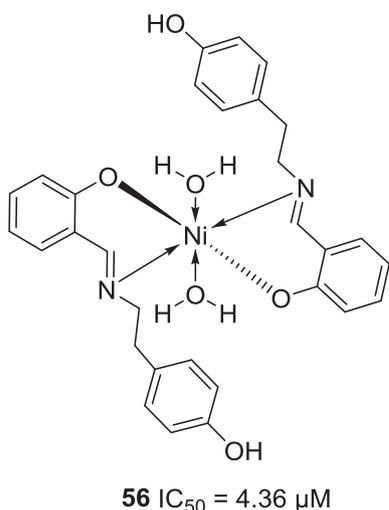
Fig. 11. Chemical structure of the nickel complex **56**.
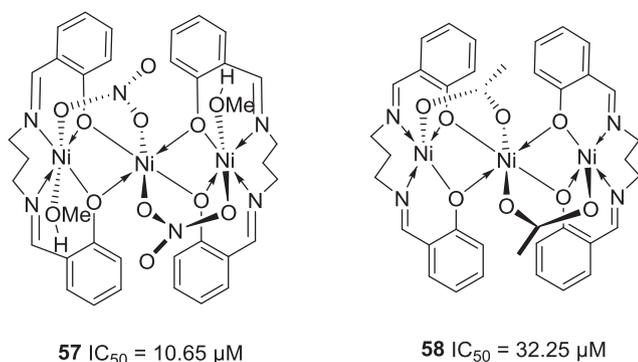

57 IC$_{50}$ = 10.65 μM   **58** IC$_{50}$ = 32.25 μM

Fig. 12. Chemical structures of hexa-coordinated complexes of Ni^{2+} synthesized by Shi and co-workers [61].
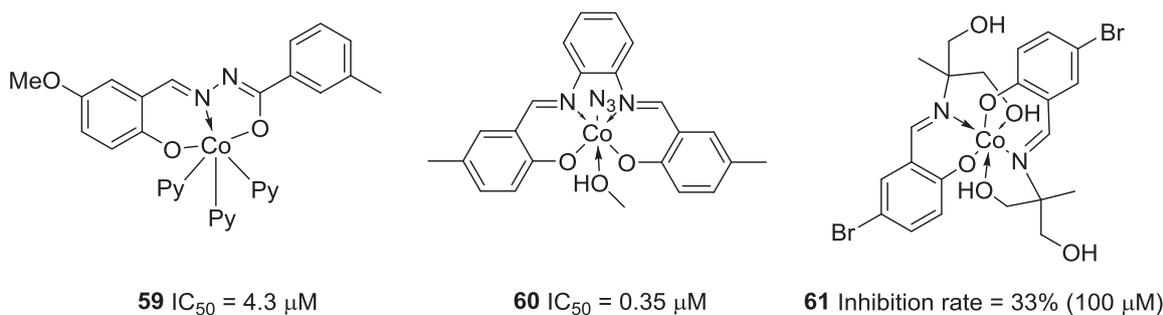
bitors of jack bean urease. They observed that those ions presented anti-urease activities by themselves, and Cu^{2+} was more effective (IC$_{50}$ = 0.37 μM) than Ni^{2+} (IC$_{50}$ = 2.87 μM), while Mn^{2+} did not have any effect on urease activity. Zhu and co-workers also compared copper complexes bearing three different Schiff bases as ligands. For instance, compound **32** (IC$_{50}$ = 2.25 μM), a dinuclear complex, was less potent than compound **33** (IC$_{50}$ = 0.43 μM), a mononuclear complex (Fig. 5). In compound **32**, each copper atom exists in a square-pyramidal configuration with five coordination sites (one site is occupied by the nitrogen atom and the other four by oxygen atoms from three *N*-salicylideneglycinate ligands). In contrast, complex **33** is a mononuclear square-pyramidal five-coordinate complex in which the apical coordination site is occupied by water. The basal plane is occupied by one oxygen atom from a phenolate group and three nitrogen atoms from the imine group, the morpholine group and the pyridine. Compound **34** (Fig. 5; IC$_{50}$ = 0.59 μM), a mononuclear tetra-coordinate complex in a *trans*-square-planar configuration, was more potent than compound **32**. The Schiff bases discussed herein act as bidentate ligands and coordinate through the oxygen atom of the *ortho*-OH group and the nitrogen atom from the imine group (Fig. 5) [38]. In 2007, Zhu and coworker also reported copper complex **35**, in addition to Ni, Zn and Co complexes, derived from Schiff bases as a potential urease inhibitor (IC$_{50}$ = 2.39 μM). Complex **35** is a four-coordinate square-planar complex, and the ligand is coordinated to the metal through two nitrogen and two oxygen atoms from the Schiff base (Fig. 5) [40].

You and co-workers (2016) synthesized nine copper complexes bearing Schiff base ligands, and of those complexes, five complexes (**36, 38–41**) had strong activities (IC$_{50}$ lower than 1 μM) against the urease of *Helicobacter pylori*. Complex **36** (Fig. 6), which had the best anti-urease activity (IC$_{50}$ = 0.03 μM), was shown to be a mixed-competitive inhibitor (K$_i$ = 15.0 μM) [41]. Pervez and co-workers (2016) also synthesized some copper complexes of isatin-derived *bis*-Schiff base ligands, and they evaluated the anti-urease activities of all synthesized complexes. Among the ser-

59 IC$_{50}$ = 4.3 μM   **60** IC$_{50}$ = 0.35 μM   **61** Inhibition rate = 33% (100 μM)

Fig. 13. Chemical structures of active anti-urease cobalt-complexes.
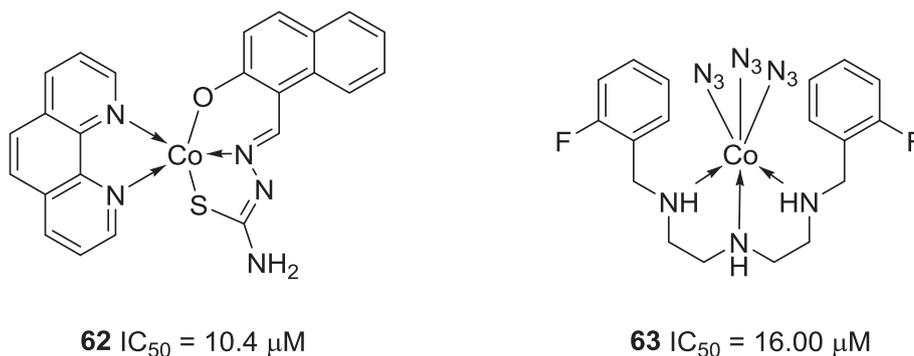

62 IC$_{50}$ = 10.4 μM   **63** IC$_{50}$ = 16.00 μM

Fig. 14. Chemical structures of the most active cobalt complexes tested against *Canavalia ensiformes* urease.

ies of obtained complexes, compound **37** stands out due its high anti-urease activity (IC$_{50}$ = 0.03 μM), which is ten-fold stronger than its own free Schiff base ligand (IC$_{50}$ = 0.34 μM) (Fig. 6) [42].

It is also important to highlight the work of Pan and co-workers (2016) (**42** and **43**), Chen and co-workers (**44** and **46**), Habala and co-workers (2016) (**45**), Dong and co-workers (2011) (**47**), Cui and co-workers (2011) (**48**) and You and co-workers (2010) (**49**), who synthesized copper complexes with IC$_{50}$ values better than 1 μM, i.e., compounds with potent activities (Fig. 7) [43–48].

Schiff base zinc complexes

Zinc is the second most abundant element in biological systems. The Zn^{2+} ion has a closed *d*-shell, which makes it a redox-stable ion. Zn^{2+} interacts with the side chains of amino acids residues in proteins/peptides and with non-protein ligands. Zinc atoms contribute to the structure and catalytic activity of metalloproteins [49–51]. Because of the diversity of its biological functions and its low toxicity [47], zinc has been a starting point for the design of urease inhibitors based on Zn-complexes. Notably, Zn^{2+} by itself has no anti-urease activity [44,52–57]; however, when it is used in the form of a zinc-complex, this metal enhances the inhibitory activity of the ligand.

Cheng and co-workers (2007) synthesized the first zinc complex bearing Schiff base ligands, and the complex was assayed as a urease inhibitor; however, it showed no anti-ureolytic activity [40]. After Cheng's zinc complex, other zinc complexes were prepared, and they have been shown to possess promising anti-urease activities. For instance, Chen and co-workers (2010) reported two Zn^{2+} complexes (**50**, IC$_{50}$ = 9.27 mM and **51**, IC$_{50}$ = 1

9.18 mM; Fig. 8) that were more potent than acetohydroxamic acid (IC$_{50}$ = 42.12 μM) in the inhibition of jack bean urease. Just like Zn^{2+}, which has no anti-urease activity, the ligands used to prepare **50** and **51** also were ineffective to inhibit such enzyme [44].

It is also important to highlight the zinc complexes obtained by You and co-workers (2009) (**52** and **53**) and Wang and co-workers (2012) (**54** and **55**); however, these complexes presented only moderate anti-urease activities (70 μM < IC$_{50}$ < 100 μM) (Fig. 9) [57,58].

Schiff base nickel complexes

Nickel plays an important role in biological systems such as urease, a strictly nickel-dependent enzyme in biological environment [59,60]. Nickel may exist in several oxidation states, and this will directly affect the formation of Ni complexes as well as their capacities to display biological effects. Ni^{2+} complexes are the most
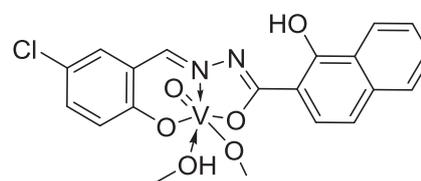
69 IC$_{50}$ = 17.35 μM

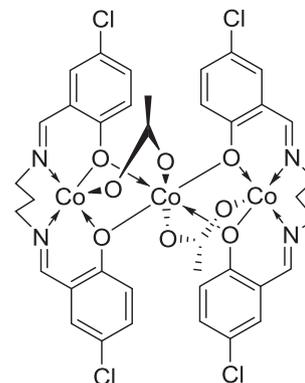**Fig. 17.** Chemical structure of vanadium complex **69**, reported by You and co-workers [80].
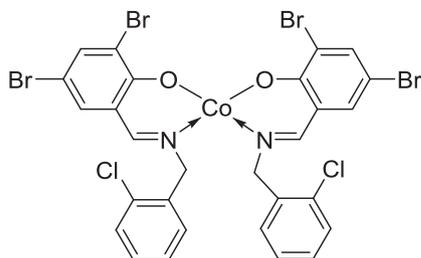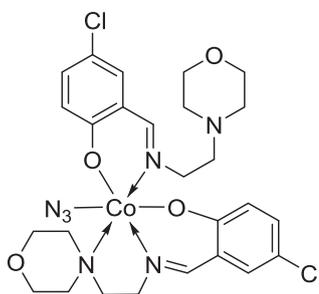
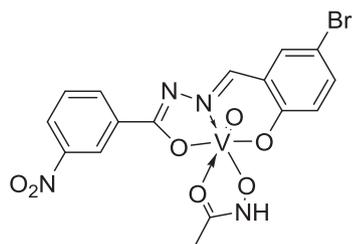**64** IC$_{50}$ = 25.20 μM   **65** IC$_{50}$ = 27.12 μM   **66** IC$_{50}$ = 45.73 μM
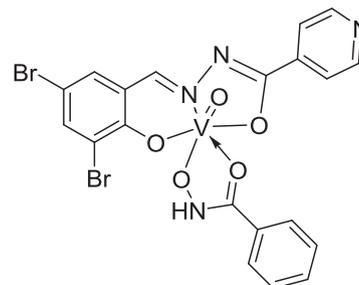
Fig. 15. Chemical structures of anti-urease cobalt complexes **64–66**.

67 IC$_{50}$ = 8.3 μM   **68** IC$_{50}$ = 10.5 μM

Fig. 16. Chemical structures of vanadium complexes **67** and **68**.

70 IC$_{50}$ = 21.5 μM

71 IC$_{50}$ = 27.32 μM

72 IC$_{50}$ = 38.05 μM

73 IC$_{50}$ = 47.89 μM

74 IC$_{50}$ = 37.7 μM

75 IC$_{50}$ = 63.6 μM

76 IC$_{50}$ = 63.3 μM

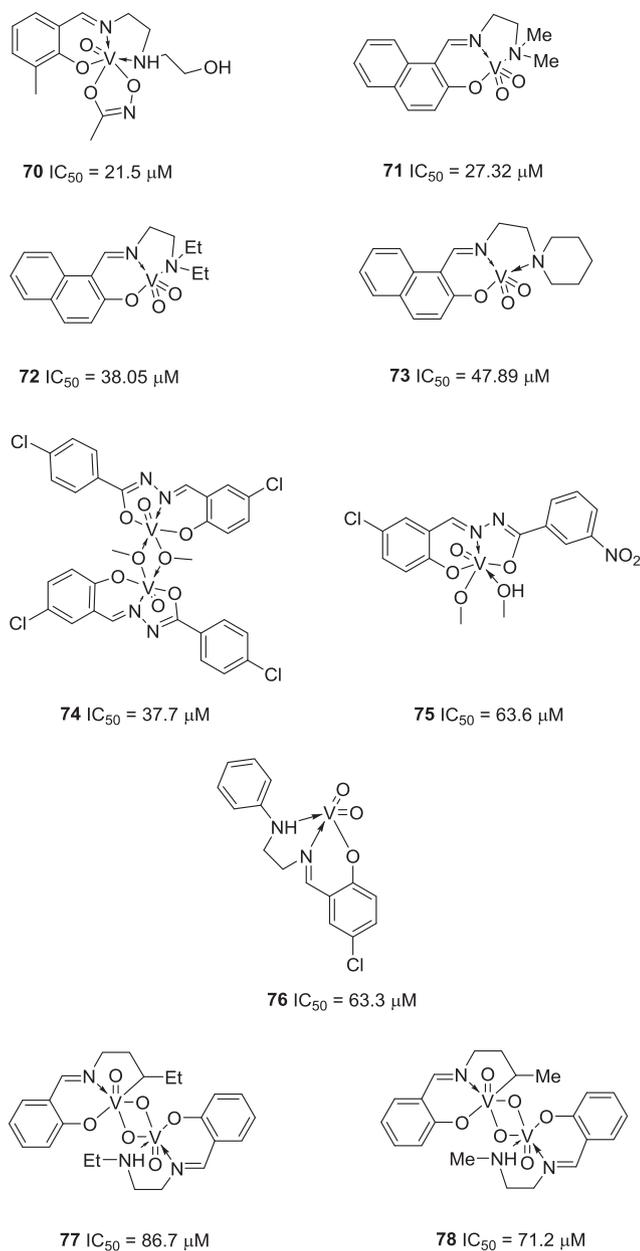**77** IC$_{50}$ = 86.7 μM

78 IC$_{50}$ = 71.2 μM

Fig. 18. Chemical structures of Schiff base vanadium complexes **70–78**, which possess anti-urease activities.

important Ni complexes in medicinal chemistry. These complexes usually adopt four- or six-coordinate three-dimensional structures (Fig. 10).

In 2007, Li and co-workers reported that free Ni^{2+} ions (IC$_{50}$ = 2. 87 μM) inhibited the ureolytic activity of purified jack bean urease; however, the observed inhibitory activity was influenced by the type of ligands present on the complexes studied. These authors also evaluated the anti-urease activity of complexes of Cu^{2+}, Ni^{2+} and Mn^{2+} ions, but nickel complex **56** (Fig. 11) presented the strongest inhibition of urease [38].

Shi and co-workers described the preparation and anti-ureolytic activity of six hexa-coordinate complexes of Ni^{2+}, Mn^{2+}, Co^{2+} and Cd^{2+} [61]. Nickel complexes **57** (IC$_{50}$ = 32.25 μM) and **58** (IC$_{50}$ = 10.65 μM) (Fig. 12) showed potent jack bean anti-urease activity with IC$_{50}$ values lower than that determined for acetohydroxamic acid (IC$_{50}$ = 42.12 μM), a positive control used for the enzymatic assay [61].

Schiff base cobalt complexes

Cobalt is one of the most studied transition metals for the inhibition of the ureolytic activity of urease enzymes. Cobalt has two common oxidation states: Co^{2+} and Co^{3+}. Co^{3+} can be found in different biological systems, such as vitamin B12, which is an essential molecule for blood cell formation and normal function of the nervous system [40,62]. Cobalt complexes have been used to fight bacteria, viruses, fungi, and tumor cells and some of them have shown strong anti-urease activities [40,63,64]. The best complexes tested against the pure urease obtained from *H. pylori* were described by Jing and co-workers and Lu and co-workers [65,66]. Jing's research group showed that complexes **59** and **60** (Fig. 13; IC$_{50}$ = 4.3 μM and 0.35 μM, respectively) can effectively inhibit urease enzymes, while Lu's group reported that Co-Schiff base complex **61** (Fig. 13) was also able to inhibit urease; however, its efficacy (33% inhibition) was lower than that observed for the ligand itself (83% inhibition).

In 2013, Qiu and co-workers reported that Co^{2+} complex **62** (IC$_{50}$ = 10.4 μM; Fig. 14), as well as the Ni^{2+}, Cu^{2+} and Zn^{2+} complex analogues, possess high anti-urease activities. They also demonstrated that these metallic complexes interact with the sulfhydryl groups of cysteines, the nitrogen atoms of histidines and/or the oxygen atoms of glutamic acid residues of the amino acids present on the urease. According to the results obtained by Qiu and co-workers, the Co^{2+} and Zn^{2+} ions had no anti-urease activities, while Ni^{2+} and Cu^{2+} were able to inhibit ureolytic activity [53]. The anti-urease activity of the complexes decreased in the order [Cu(L)] > [Co(L)] > [Ni(L)], while the zinc complexes had no anti-urease

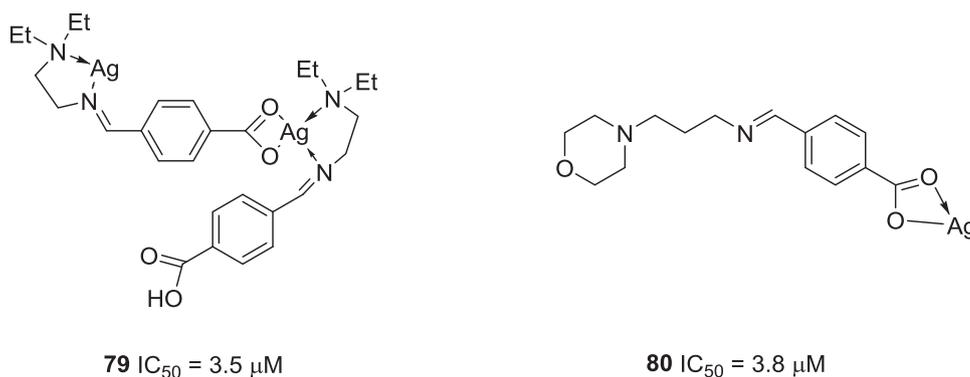**79** IC$_{50}$ = 3.5 μM

80 IC$_{50}$ = 3.8 μM

Fig. 19. Chemical structures of silver complexes **79** and **80** reported by Zhang and co-workers [86].

activities [53]. Notably, the trend in the anti-urease activities observed for the metals by themselves did not match the trend in the activities of the complexes. For instance, Ni^{2+} and Cu^{2+} ions were not able to inhibit urease enzyme; however, their complexes were effective. On the other hand, Zn^{2+} inhibited urease, but its complexes were inactive. Dong and co-workers also synthesized highly active Co complex **63** (IC_{50} = 16.00 μM), and its anti-urease activity was attributed to its interaction with the metallic center and the sulfhydryl moieties of cysteine residue close to the enzyme's active site [46].

Other notable contributions to cobalt complex urease inhibitors were made by Chen and co-workers (2010) (**64**), Wang (2010) (**65**) and You and co-workers (2007) (**66**) (Fig. 15). Many of the cobalt complexes synthesized by these research groups were effective against urease and showed IC_{50} values similar to those of acetohy-

droxamic acid, a positive control used in the anti-urease assays [44,67,68].

Vanadium complexes

Vanadium, a transitional metal, exists in oxidation states including −3, −1, 0 and +1 to +5, but +4 and +5 are the most common states in biological systems, and V ions are usually bound to proteins [69,70]. The main biological activities of vanadium complexes are related to diabetes due its ability to enhance the production of insulin [69–72]. Other bioactivities described for such complexes are antitumor [73–75], antibacterial [76,77], antifungal [76] and antioxidant activities [77] as well as anti-urease properties, and these activities were primarily observed while aiming to develop new anti-*Helicobacter pylori* agents.

81 IC_{50} = 6.28 μM

82 IC_{50} = 8.3 μM

83 IC_{50} > 100 μM

84 Inhibition rate = 57.8% (100 μM)

85 Inhibition rate = 49.0% (100 μM)
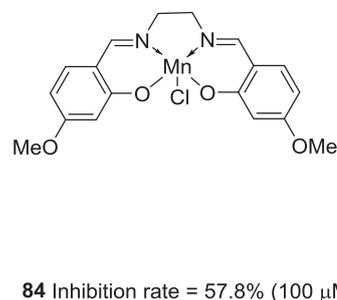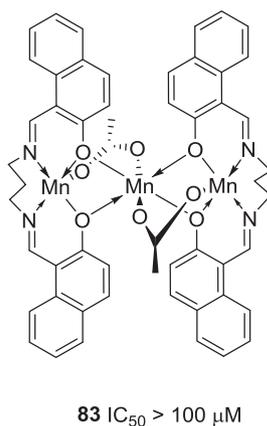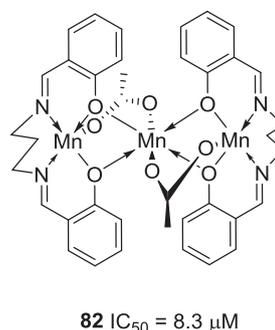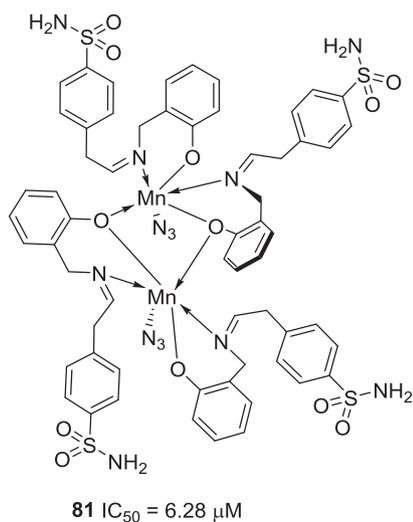
86 Inhibition rate = 49.4% (100 μM)
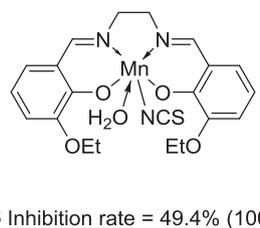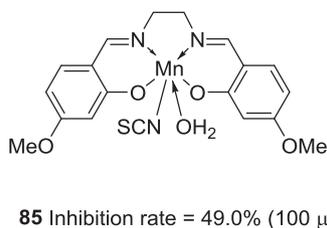
Fig. 20. Chemical structures of penta and hexa-coordinated Schiff base manganese complexes **81–86**.

In 2014, Huo and co-workers reported the anti-urease activity ($IC_{50} = 8.3 \mu M$) of vanadium complex **67** and disclosed that it is a mixed inhibitor [78] (Fig. 16). In the same year, Sheng and co-workers prepared new Schiff base oxovanadium complex **68**, which also showed promising urease inhibitor activity ($IC_{50} = 10.5 \mu M$) [79] (Fig. 16). Both complexes have the same metal coordination geometry differing only by the types of the ligands present; however, these modifications lead to slight variations in their inhibitory potency.

You and co-workers synthesized six vanadium complexes with Schiff base ligands that were prepared with different imines but with the same hydroxyl group present on the aldehyde. Among these complexes, **69**, a mixed inhibitor ($Ki = 99 \mu M$), was the most active vanadium Schiff base complex ($IC_{50} = 17.35 \mu M$) [80] (Fig. 17).

Among all vanadium Schiff base complexes described, the most active anti-urease complexes (Fig. 18) are those reported by Ren and co-workers (2014) (**70**; $IC_{50} = 21.5 \mu M$), You and co-workers (2011) (**71**–**73**; $IC_{50} = 27.32 \mu M$, 38.05 μM and 47.89 μM, respectively), Zhao and co-workers (2013) (**74** and **75**; $IC_{50} = 37.7 \mu M$ and 63.6 μM, respectively), You and co-workers (2012) (**76**; $IC_{50} = 63.3 \mu M$) and You and co-workers (2011) (**77** and **78**. $IC_{50} = 86.7 \mu M$ and 71.2 μM, respectively) [81–85].

Other metals complexes

In addition to the Schiff base complexes mentioned above, other complexes bearing silver, manganese, cadmium, iron and rhodium ions have been described as potential anti-urease agents. For instance, Zhang and co-workers (2017) synthesized two silver complexes, **79** and **80** (Fig. 19), which showed potent anti-urease activities ($IC_{50} = 3.5$ and 3.8 μM, respectively) [86]. However, in both cases no improvement in the anti-urease activity was observed when the metal was present as the complex since the metal by itself showed the same level of anti-urease activity ($IC_{50} = 3.5 \mu M$) [86].

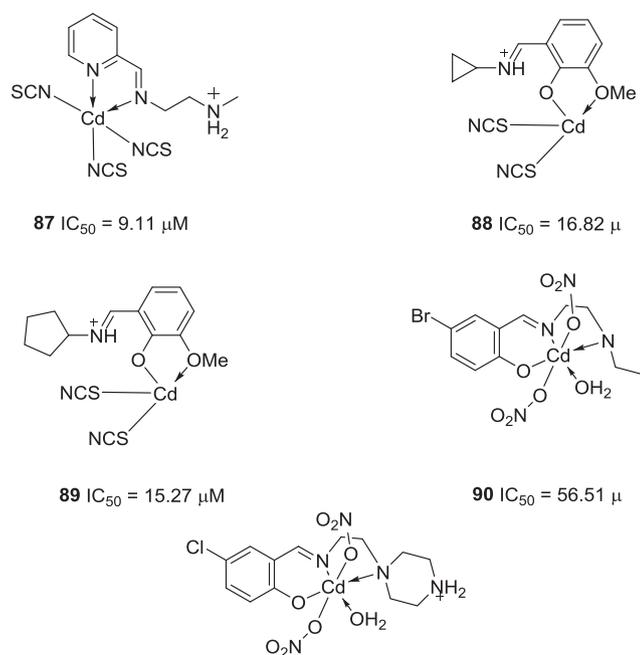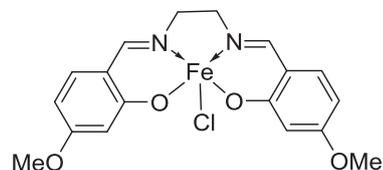Some examples of manganese complexes with anti-urease activities were described by Li and co-workers (2007). According

92 Inhibition rate = 39.5% (100 μM)

Fig. 22. Chemical structure of Schiff base iron complex reported by Shi et al., 2012 as urease inhibitor.

to these authors, bimetallic manganese complex **81** (Fig. 20) was the most active showing an IC_{50} value of 6.28 μM ($IC_{50} = 42.12 \mu M$ for acetohydroxamic acid, the positive control) (38)]. In the same year, Shi and co-workers reported trimetallic manganese complexes **82** ($IC_{50} = 8.3 \mu M$) and **83** ($IC_{50} > 100 \mu M$) (Fig. 20; the IC_{50} for the positive control was 42.12 μM) [61]. Other manganese complexes (**84**–**86**; Fig. 20) were also reported as urease inhibitors; however, these complexes showed low potencies (inhibition rates less than 60% at 100 μM) [87,88].

In the case of the cadmium, notable complexes include **87**, **88** and **89** (Fig. 21), which were reported by You and co-workers (2008). These complexes showed IC_{50} values equal to 9.1 μM, 16.8 μM and 15.3 μM, respectively. However, in those cases, the cadmium salt by itself was also a very potent urease inhibitor ($IC_{50} = 19.3 \mu M$) [89]. Other Schiff base cadmium complexes (**90** and **91**, Fig. 21) were reported by Shi and co-workers (2010) [90]; however, they showed lower activities than acetohydroxamic acid ($IC_{50} = 42.12 \mu M$), a positive control used as a urease inhibitor.

The iron Schiff base complexes are among the least explored as urease inhibitors. The most active iron complex that has been described is **92** (Fig. 22), but it showed an inhibition rate of only 39.5% at 100 μM. Because of its low activity, the IC_{50} value for **92** was not determined [87].

Patents of Schiff bases as urease inhibitors

In 2015, a series of 27 thiazole Schiff bases (Fig. 23) was found to exhibit anti-urease activity and was patented by Choudhary and co-workers [91,92]. These authors described a complete study, which included a kinetic analysis of the 10 most potent thiazole Schiff base derivatives. Of all the evaluated substances, the most potent inhibitor was thiazole **93**, which presented an IC_{50} value of 2.80 μM [91].

In addition to Choudhary's patent, there is only one other relevant patent; that patent is from de Fátima's research group in 2016, and it describes the inhibitory activities of 71 Schiff bases (Fig. 24) against urease. de Fátima and co-workers also described a method for producing urea pearls combined with aldimines (Schiff bases), which were used to inhibit soil urease to enhance the growth and development of crops by using urea-based fertilizers [93]. Among the tested Schiff bases, **94** showed the best activity against a urease purified from *Canavalia ensiformis*.

Conclusions and future perspectives

Schiff bases have been widely explored for medical and industrial applications. However, the antiurease activities of this class of compounds deserves more investigation. As herein highlighted, substances bearing conjugated unsaturated systems and/or heteroatoms play an important role on the urease inhibitors efficacy. In addition, it seems that, within the scope of our review, the coordination of Schiff bases with metals results in improvement

87 $IC_{50} = 9.11 \mu M$

88 $IC_{50} = 16.82 \mu$

89 $IC_{50} = 15.27 \mu M$

90 $IC_{50} = 56.51 \mu$

Fig. 21. Chemical structures of tetra, penta and hexa-coordinated Schiff base cadmium complexes **87**–**91**.

of the potency of the free bases. Copper(II) is the most widely studied metal and showed the best IC_{50} values for urease inhibition. Despite the previously reported promising anti-urease activities described for Schiff bases and Schiff base metal complexes, the research on this subject is incipient. The number of reports disclosing the effects of Schiff bases and/or their metal complexes on purified urease from *Canavalia ensiformis* has increased; however, the effects of such substances on urease from *H. pylori*

require further investigation. The study of Schiff bases and/or their metal complexes has proven in the past decades be a golden mine of effective anti-ureolytic agents with potential to treat diseases caused by urease-dependent pathogenic microorganisms. However, advances in this field will require analyses of Schiff base structure-activity relationships, particularly for the Schiff base metal complexes, as well as the mechanism of action of these compounds.
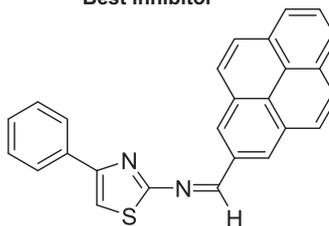
General structure:
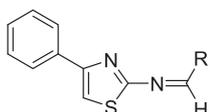
R = 3-1H-indolyl; 2-OH-3-OC$_2$H$_5$-C$_6$H$_3$; 4-OC$_2$H$_5$-C$_6$H$_4$; 4-pyridyl; 2-OH-3-OCH$_3$-C$_6$H$_3$; 2-naphthyl; 2-OH-5-Cl-C$_6$H$_3$; 4-CH(CH$_3$)$_2$-C6H$_4$; 5-CH$_3$-2-furanyl; 4-NO$_2$-C$_6$H$_4$; 4-OH-C$_6$H$_4$; 4-OCH$_3$-C$_6$H$_4$; 4-N(CH$_3$)$_2$-C$_6$H$_4$; 2-OH-C$_6$H$_4$; (CH)$_2$-4-OCH$_3$-C$_6$H$_4$; 4-SCH$_3$-C$_6$H$_4$; C$_6$H$_5$; 2-Cl-C$_6$H$_4$; 1-naphthyl; 2-F-C$_6$H$_4$; 2,3-OH-C$_6$H$_3$; 3,4-OCH$_3$-C$_6$H$_3$; 2,6-Cl-C$_6$H$_3$, 4-Cl-C$_6$H$_4$; 2,3,4-OCH$_3$-C$_6$H$_2$ or 3-NO$_2$-C$_6$H$_4$.

Standard inhibitor used: thiourea (IC_{50} = 20.43 μM)

Inhibition range: (IC_{50} = 2.80 to 36.66 μM)

Best inhibitor

93 IC_{50} = 2.80 μM

Fig. 23. Chemical structures of Schiff bases, synthesized by de Choudhary's research group, which possess anti-urease activities.

General structure:
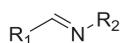
R$_1$ = C$_6$H$_5$; 2-OH-C$_6$H$_4$; 3-OH-C$_6$H$_4$; 4-OH-C$_6$H$_4$; 2,3-(OH)$_2$-C$_6$H$_3$; 2,5-(OH)$_2$-C$_6$H$_3$; 3,4-(OH)$_2$-C$_6$H$_3$; 2,3,4-(OH)$_3$-C$_6$H$_2$; 2-pyridyl; 4-F-C$_6$H$_4$; 2-furanyl; 3-NO$_2$-2-furanyl; 5-1,2-dioxolyl-C$_6$H$_3$; 3,6-(SO$_3$H)$_2$-8-OH-naphthyl; (CH)$_2$-C$_6$H$_5$; (CH)$_2$-4-OCH$_3$-C$_6$H$_4$; (CH)$_2$-2-NO$_2$-C$_6$H$_4$; (CH)$_2$-4-OCH$_3$-C$_6$H$_4$ and/or (CH)$_2$-4-N(CH$_3$)$_2$-C$_6$H$_4$.

R$_2$ = C$_6$H$_5$; 2-OH-C$_6$H$_4$; 3-OH-C$_6$H$_4$; 4-OH-C$_6$H$_4$; 4-OCH3-C$_6$H$_4$; 4-Cl-C$_6$H$_4$; 4-CN-C$_6$H$_4$; 2-CN-C$_6$H$_4$; 4-SCH3-C$_6$H$_4$; 4-F-C$_6$H$_4$; 4-CF3-C$_6$H$_4$ and/or 1-adamantanyl.

Standard inhibitor used: hydroxyurea (63% inhibition, 500 μM)

Inhibition range: 0 to 90% inhibition, 500 μM

Best inhibitor

94 Inhibition rate = 90% (500 μM)

Fig. 24. Chemical structures of Schiff bases, synthesized by de Fátima's research group, which possess anti-urease activities.

Conflict of interest
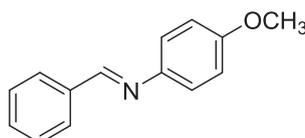
The authors have declared no conflict of interest.

Compliance with Ethics requirements

This article does not contain any studies with human or animal subjects.

Acknowledgements

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