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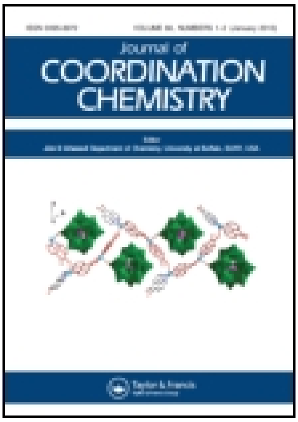

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Synthesis and biological evaluation of Cu(II), Zn(II), and Ni(II) 3-(4-nitrophenyl)acrylic acid complexes with diamines as potential urease inhibitors

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Synthesis and biological evaluation of Cu(II), Zn(II), and Ni(II) 3-(4-nitrophenyl)acrylic acid complexes with diamines as potential urease inhibitors

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Five new Cu(II), Zn(II), and Ni(II) 3-(4-nitrophenyl)acrylic acid complexes were synthesized and evaluated for inhibitory activity on *jack bean* urease. All five complexes were structurally determined by single crystal X-ray analysis. Compared with the positive reference acetohydroxamic acid ($IC_{50} = 13.25\ \mu M$), Cu(II) complexes **3** and **4** showed the strongest inhibitory activity against *jack bean* urease ($IC_{50} = 1.23$ and $1.17\ \mu M$). Ni(II) and Zn(II) complexes also exhibited inhibitory activities ($IC_{50} = 10.09$–$13.10\ \mu M$).

Keywords: Urease inhibitor; Cinnamate; Transition metal complex; Crystal structure

1. Introduction

Urease is widely found in a variety of organisms such as plants, fungi, algae, and bacteria [1, 2]. This enzyme is regarded as a virulent factor in human and animal infections of the urinary and gastrointestinal tracts. It may cause urolithiasis, pyelonephritis, chronic gastritis, duodenal ulcer, gastric ulcer, and even gastric cancer [3, 4].

Urease (EC 3.5.1.5) is an enzyme containing two nickel(II) ions in its active site [5]. It can catalyze the hydrolysis of urea into ammonia and carbamate, and the carbamate spontaneously hydrolyzes at physiological pH to form carbonic acid and a second molecule of ammonia [6]. Comparing the sequences of *jack bean* urease and bacteria urease suggests that these two different kinds of urease may have a common evolutionary origin [7]. Because the catalytic site displayed highly conserved amino acid residues, *jack bean* urease and *Helicobacter pylori* (*H. pylori*) urease may have the same catalytic mechanism.

Urease is the major cause of pathologies induced by *H. pylori* as it allows the bacteria to survive in the extremely acidic environment of stomach during colonization. So, the high level of urease activity is one of the most important characteristics of *H. pylori* [8–11]. Several classes of compounds show significant inhibitory activity against urease with hydroxamic acids being the best recognized inhibitors [12]. The urease inhibitors used

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*Corresponding author. Email: hailiang_zhu@163.com to have strong side effects [13], thus we must search for new urease inhibitors with good bioavailability and low toxicity.

Cinnamic acid derivatives have been demonstrated to have many pharmacological effects such as anticancer, antioxidant, antityrosinase, and antihyperglycemic activity [14]. Our research group has reported many Schiff base transition metal complexes as urease inhibitors [15–18]. In this research, we replaced the Schiff base ligands in previous articles with 3-(4-nitrophenyl)acrylic acid and synthesize new transition metal complexes. The synthesis, crystal structure, and urease inhibitory activities of new copper(II), zinc(II), and nickel(II) 3-(4-nitrophenyl)acrylic acid complexes with N,N-dimethylethylenediamine, ethylenediamine, or 1,2-propanediamine are reported in this paper.

2. Experimental

2.1. *Materials and measurements*

p-Nitrobenzaldehyde, 1,2-propanediamine, and N,N-dimethylethylenediamine were purchased from Aladdin and used without purification. *Jack bean* urease was purchased from Sigma-Aldrich Co. (St. Louis, MO, USA), while other reagents and solvents were purchased from commercial suppliers. The crystal structures of **1**–**5** were determined by a Thermo Nicolet 5700 spectrometer and Bruker D8 Venture single crystal diffraction.

2.2. *Complexe synthesis*

3-(4-Nitrophenyl)acrylic acid was prepared by the reaction of *p*-nitrobenzaldehyde ($C_8H_7NO_3$) with malonic acid ($C_3H_3O_4$) in ethanol using pyridine (C_5H_5N) as catalyst. After purification, the yield of 3-(4-nitrophenyl)acrylic acid ($C_9H_7NO_4$) was 73%. The purified 3-(4-nitrophenyl)acrylic acid was then dissolved in water and NaOH (0.01 M/L) was added to change the solution pH to 7. $MSO_4 \cdot nH_2O$ (M=Cu, $n = 5$; M=Zn, Ni, $n = 7$)

Table 1. Crystallographic and experimental data for **1**–**5**.

Complexes	**1**	**2**	**3**	**4**	**5**
Empirical formula	$C_{22}H_{31}N_4O_{11}Ni$	$C_{22}H_{28}N_6O_{12}Ni$	$C_{26}H_{50}N_6O_{16}Cu_2$	$C_{22}H_{38}N_6O_{12}Cu$	$C_{21}H_{22}N_4O_8Zn$
Molecular weight	586.20	637.27	829.82	642.13	523.82
Crystal system	Triclinic	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space group	*P*-1	*C*2/*c*	*P*-1	*C*2/*c*	*Pnma*
a (Å)	6.2331(5)	31.0943(17)	7.5763(7)	31.0826(13)	6.0983(2)
b (Å)	14.2263(11)	6.5008(4)	8.0475(7)	6.0511(3)	25.9204(9)
c (Å)	15.0427(12)	14.6306(8)	15.7825(14)	14.6480(7)	13.9274(4)
α (°)	77.244(3)	90	77.404(3)	90	90
β (°)	82.061(3)	105.478(2)	76.433(3)	105.535(2)	90
γ (°)	81.259(3)	90	79.479(3)	90	90
V (Å^3)	1278.28(18)	2850.1(3)	904.10(14)	2851.8(2)	2201.51(12)
Z	2	4	1	4	4
ρ_{Calcd} (g cm^{-3})	1.523	1.485	1.524	1.495	1.580
F (0 0 0)	614	1344	434	1348	1080
μ (Mo-Kα) (mm^{-1})	0.826	0.751	1.253	0.837	1.173
Theta min/max	2.23/26.00	3.2/30.6	2.62/25.99	3.21/25.00	2.93/25.00
R_1, ωR_2 [$I > 2\sigma(I)$]	0.0983, 0.2667	0.0245, 0.0654	0.0401, 0.1028	0.0282, 0.0762	0.0321, 0.0833
Goodness of fit on F^2	1.025	1.052	1.048	1.040	1.065

was dissolved in water and then added into the solution from the last step. Precipitate was filtered and dried after 20 min stirring. Three kinds of diamine ammonia methanol solutions (0.1 mM/mL) were added to a methanol solution (0.1 mM/mL) of 3-(4-nitrophenyl) acrylic acid metal salt in different ratios. Another 10 mL methanol was added and stirred for another 15–20 min at room temperature and then filtered. The filtrate was evaporated for one week and single crystals were precipitated, isolated, and washed with water three times and dried in a vacuum desiccator under $CaCl_2$.

Table 2. Selected bond lengths [Å] and angles [°] in **1**–**5**.

1			
Ni1–O3	2.032(5)	Ni1–O9	2.138(5)
Ni1–O10	2.112(5)	Ni1–O11	2.150(6)
Ni1–N3	2.156(7)	Ni1–N4	2.063(6)
O3–Ni1–O9	83.19(19)	O3–Ni1–O10	93.45(19)
O3–Ni1–O11	93.6(2)	O3–Ni1–N3	92.3(2)
O3–Ni1–N4	174.3(2)	O9–Ni1–O10	171.6(2)
O9–Ni1–O11	83.0(2)	O9–Ni1–N3	97.4(2)
O9–Ni1–N4	93.2(2)	O10–Ni1–O11	89.6(2)
O10–Ni1–N3	90.4(2)	O10–Ni1–N4	90.7(2)
O11–Ni1–N3	174.1(2)	O11–Ni1–N4	90.4(3)
N3–Ni1–N4	83.8(3)		
2			
Ni1–N2	2.0136(13)	Ni1–N3	2.0136(13)
Ni1–N2A	2.0136(13)	Ni1–N3A	2.0136(13)
N2–Ni1–N3	84.32(5)	N2–Ni1–N2A	94.17(5)
N2–Ni1–N3A	170.15(5)	N3–Ni1–N2A	170.15(5)
N3–Ni1–N3A	98.79(5)	N2A–Ni1–N3A	84.32(5)
3			
Cu1–O5	1.9800(18)	Cu1–O6	2.372(2)
Cu1–O5A	1.9572(17)	Cu1–N2	2.005(2)
Cu1–N3	2.067(2)	O5–Cu1–O6	93.08(8)
O5–Cu1–N2	95.69(9)	O5–Cu1–N3	174.23(8)
O5–Cu1–O5A	82.85(7)	O6–Cu1–N2	90.97(9)
O6–Cu1–N3	92.62(9)	O6–Cu1–O5A	93.29(8)
N2–Cu1–N3	85.11(10)	N2–Cu–O5A	175.57(9)
N3–Cu1–O5A	95.93(8)		
4			
Cu1–N2	2.0120(18)	Cu1–N3	2.0117(19)
Cu1–N2A	2.0120(18)	Cu1–N3A	2.0117(19)
Cu1–O5	2.6394(16)	Cu1–O5A	2.6394(16)
N2–Cu1–N3	84.42(8)	N2–Cu1–N3A	170.13(7)
N2–Cu1–N2A	94.24(7)	N3–Cu1–N3A	98.54(8)
N3–Cu1–N2A	170.13(7)	N2A–Cu1–N3A	84.42(8)
O5–Cu1–N2	84.78(6)	O5–Cu1–N3	89.57(6)
O5–Cu1–N2A	100.06(6)	O5–Cu1–N3A	85.82(6)
O5–Cu1–O5A	172.94(4)	N2– Cu1–O5A	100.06(6)
N3–Cu1–O5A	85.82(6)	O5A–Cu1–N2A	84.78(6)
O5A–Cu1–N3A	89.57(6)		
5			
Zn1–O3	1.9432(17)	Zn1–O3A	1.9432(17)
Zn1–N3	2.017(3)	Zn1–N4	2.052(3)
O3–Zn1–N3	123.00(6)	O3–Zn1–N4	111.46(6)
O3–Zn1–O3A	100.15(7)	N3–Zn1–N4	87.18(10)
N3–Zn1–O3A	123.00(6)	N4–Zn1–O3A	111.46(6)

Compound **1** is a green solid, yield: 13.2 mg (29.79%). Compound **2** is a transparent blackish green solid, yield: 22.5 mg (50.79%). Compound **3** is a sky blue solid, yield: 13.9 mg (31.02%). Compound **4** is a violet solid, yield: 36.5 mg (81.47%). Compound **5** is a transparent light yellow solid, yield: 34.2 mg (76.17%).

2.3. *Crystal structure determinations*

The crystal structure data for **1**–**5** were collected at 293(2) or 296(2) K using Bruker D8 Venture single crystal diffraction. The collected data were reduced using SAINT [19] and empirical absorption corrections were performed using SADABS [20]. The structures were solved by direct methods and refined against F^2 by full-matrix least-squares using *SHELXTL* 97 [21]. All nonhydrogen atoms were refined anisotropically. All hydrogens were placed in geometrically ideal positions and constrained to ride on their parent. The crystallographic data for **1**–**5** are summarized in table 1. Selected bond lengths and angles are given in table 2.

IR spectra were recorded on a Thermo Nicolet 5700 spectrometer from 4000 to 400 cm^{-1}. From infrared spectra of **1**–**5**, the strong broad absorption in the 1600–1455 cm^{-1} region corresponds to the benzene ring and another strong band at 1340 cm^{-1} is due to nitro group. Some absorptions between 3355 and 2849 cm^{-1} correspond to the coordinated diamine ($-NH_2$ and $-CH_2-$). The IR spectrum supported the crystal structures of **1**–**5** [22].

2.4. *Measurement of inhibitory activity against jack bean urease*

Jack bean urease was purchased from Sigma–Aldrich Co. (St. Louis, MO, USA). The methods followed were introduced by Tanaka *et al*. [11]. The assay mixture, containing 25 µL (10 kU/L) of *jack bean* urease and 25 µL of the tested complexes of various concentrations (dissolved in solution of $DMSO : H_2O = 1 : 1$ (v/v)), was preincubated for one hour at 37 °C in a 96-well assay plate. After preincubation, 200 µL of 100 mM HEPES (N-[2-hydroxyethyl]piperazine-N′-[2-ethanesulfonic acid]) buffer [23], pH = 6.8 containing 500 mM urea and 0.002% phenol red, were added and incubated at 37 °C. The reaction time was measured by micro plate reader at 570 nm, which was required to produce enough ammonium carbonate to raise the pH of a HEPES buffer from 6.8 to 7.7, the end point being determined by the color of the phenol red indicator [24].

Table 3. Inhibition of *jack bean* urease by **1**–**5**, 3-(4-nitrophenyl)acrylic acid and acetohydroxamic acid.

Tested materials	IC_{50} (µM)
1	10.09
2	10.44
3	1.23
4	1.17
5	13.10
3-(4-Nitrophenyl)acrylic acid	17.25
Acetohydroxamic acid*	13.25

*Used as a positive control.

The inhibitory activity of 3-(4-nitrophenyl)acrylic acid was also tested against *jack bean* urease (25 µL, 10 kU/L) using urea (500 mM) in HEPES buffer (200 µL, 100 mM; pH = 6.8) (table 3).

3. Results and discussion

3.1. *Crystal structure description*

Crystal structures of **1**–**5** are shown in figures 1–5, respectively. Single crystal X-ray diffraction reveals that **1**, **2**, **4**, and **5** are mononuclear, while **3** is binuclear.

3.1.1. Description of 1. As shown in figure 1, nickel(II) is in a slightly distorted octahedral geometry with two nitrogens from N,N-dimethylethylenediamine, one oxygen from 3-(4-nitrophenyl)acrylic acid, and three oxygens from water. The bond distances of Ni1–N3 and Ni1–N4 are 3.156(7) and 2.063(6) Å, while the bond distances between Ni1 and O3, O9, O10, and O11 are 2.032(5), 2.138(5), 2.112(5) and 2.150(6) Å, respectively. The angles subtended at nickel(II) of the distorted octahedron (NiN_2O_4) are 83.0(2)–174.3(2)°.

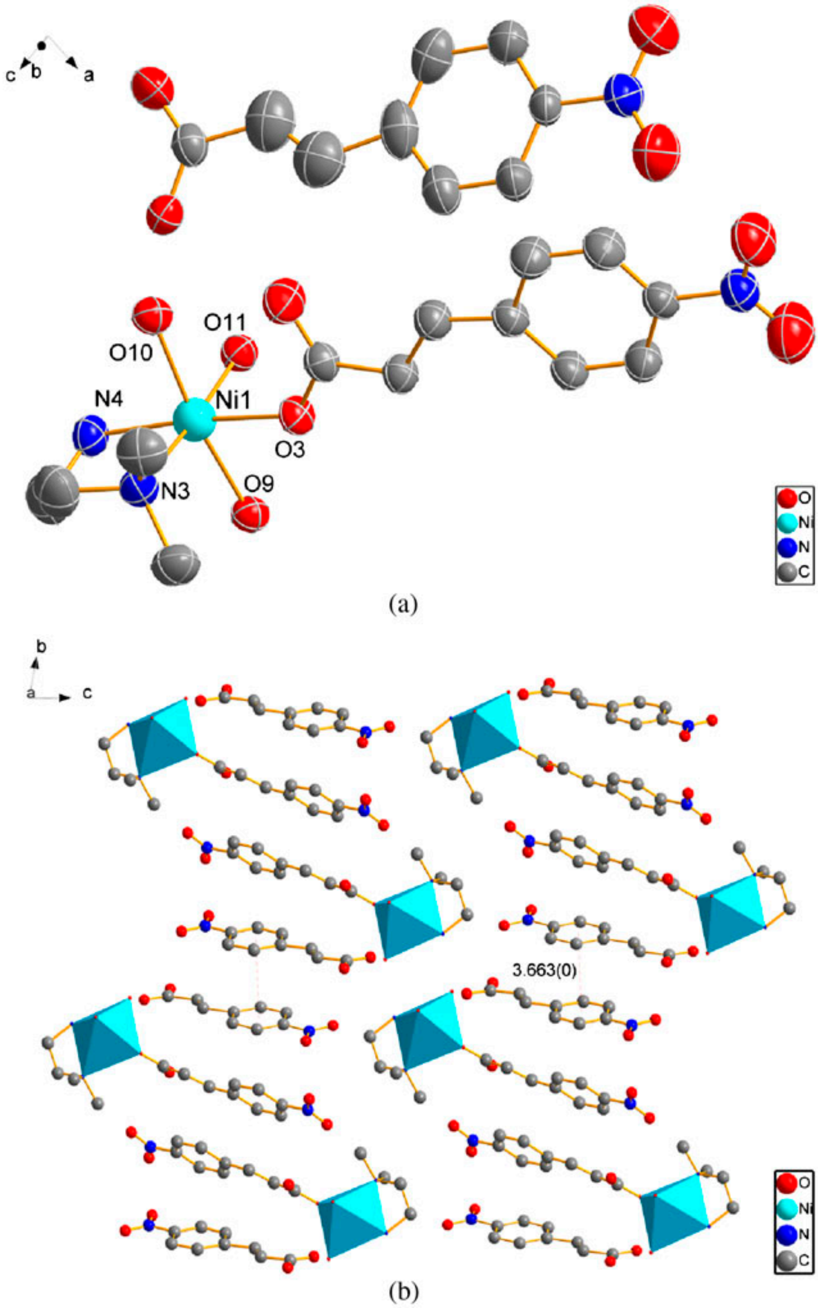
Furthermore, from the packing diagram, we find three kinds of hydrogen bonds connecting molecules. They are O9–H···O11 (symmetry code: $1-x$, $-y$, $1-z$; bond distance: 2.841(8) Å), O7–H···O9 (symmetry code: $-1+x$, y, z; bond distance: 2.761(7) Å), and O11–H···O8 (symmetry code: $1+x$, y, z; bond distance: 2.674(9) Å). Besides the hydrogen bonds, π–π stacking interactions between two benzene rings from two different 3-(4-nitrophenyl)acrylic acids which are not coordinated with the nickel(II) help connect the complex into a whole (see figure 1(b)).

3.1.2. Description of 2. Complex **2** (figure 2) is a mononuclear structure with two guest water molecules in a symmetry unit. Nickel(II) is in a distorted octahedral geometry with four nitrogens from two ethylenediamines in the basal plane, while O5 and O5A display an axial–equatorial mode of bonding. The bond distance between Ni1 and O5 is 2.6397 (14) Å and the bond distance between Ni1 and N2/N3 are both 2.0136(13) Å.

From the packing diagram, we can easily find that water bridges different units through hydrogen bonds. O6 (water) participated in two kinds of H-bonds, they are O6–H...O5 (x, $1-y$, $1/2+z$; 2.7883(18) Å) and O6–H...O4 ($-x$, $-1+y$, $1/2-z$; 2.7206 (18) Å) (see figure 2).

3.1.3. Description of 3. Compound **3** is binuclear, containing a twofold symmetry axis. Each copper(II) is in a slightly distorted pyramidal geometry, coordinated by two nitrogens from N,N-dimethylethylenediamine and two oxygens defining the basal plane, and another oxygen occupying the apical position. O5 and O5A bridge two symmetry-related copper (II). The average bond distances of Cu1–N and Cu1A–N are both 2.036(2) Å and the average bond distance between Cu1–O and Cu1A–O are both 2.103(2) Å.

In the packing diagram, there are six kinds of hydrogen bonds. O7–H···O3 (2.884(4) Å), O7–H···O8 (2.778(4) Å), and O8–H···O3 (2.746(4) Å) have the same symmetry code $1-x$, $-y$, $1-z$. Other three H-bonds are O6–H···O4 (x, $1+y$, z; 2.722(4) Å), O6–H···O7 ($-x$, $1-y$, $1-z$; 2.849(4) Å), and O8–H···O5 ($1-x$, $1-y$, $1-z$; 2.760(3) Å), respectively.

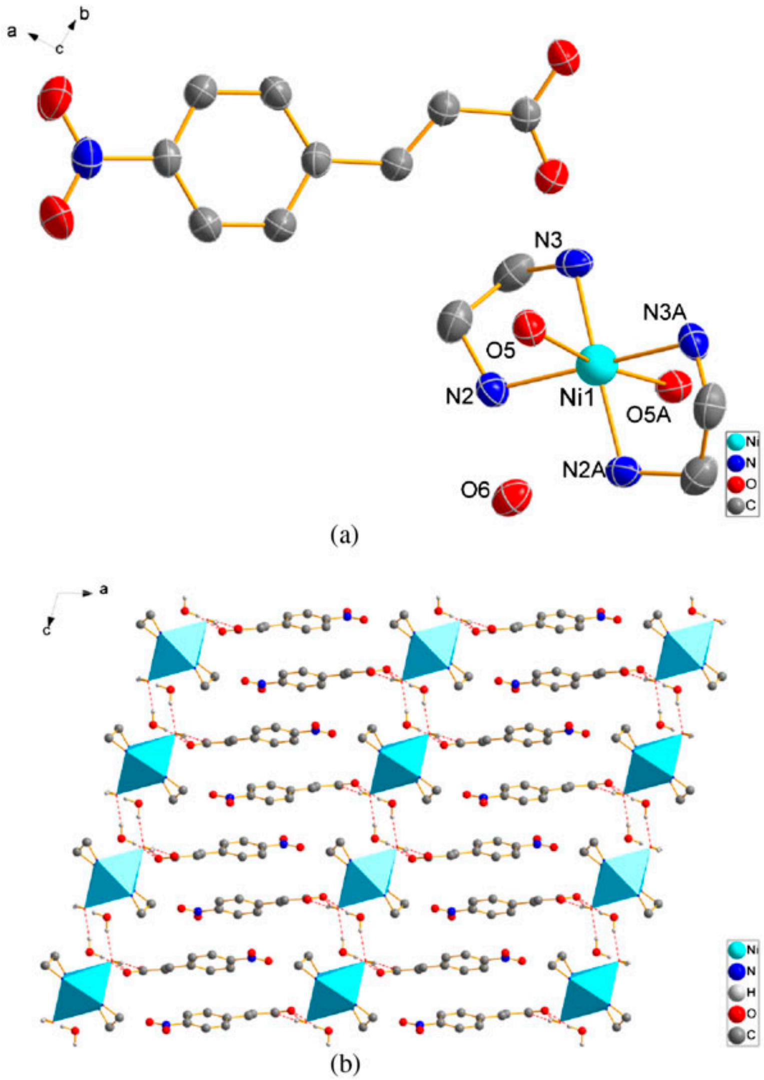


(a)

(b)

Figure 1. (a) Coordination environment of Ni in **1** drawn at 50% probability. All hydrogens are omitted for clarity. (b) The packing diagram of **1** along the *a*-axis and *π*–*π* stacking interactions between benzene rings are shown labeled with distance.

3.1.4. Description of 4. As can be seen from figure 4, the structure of **4** is similar to **2**. The copper is coordinated with two ethylenediamines in a slightly distorted octahedron. Four nitrogens form the basal plane and the two oxygens occupy the apical positions.



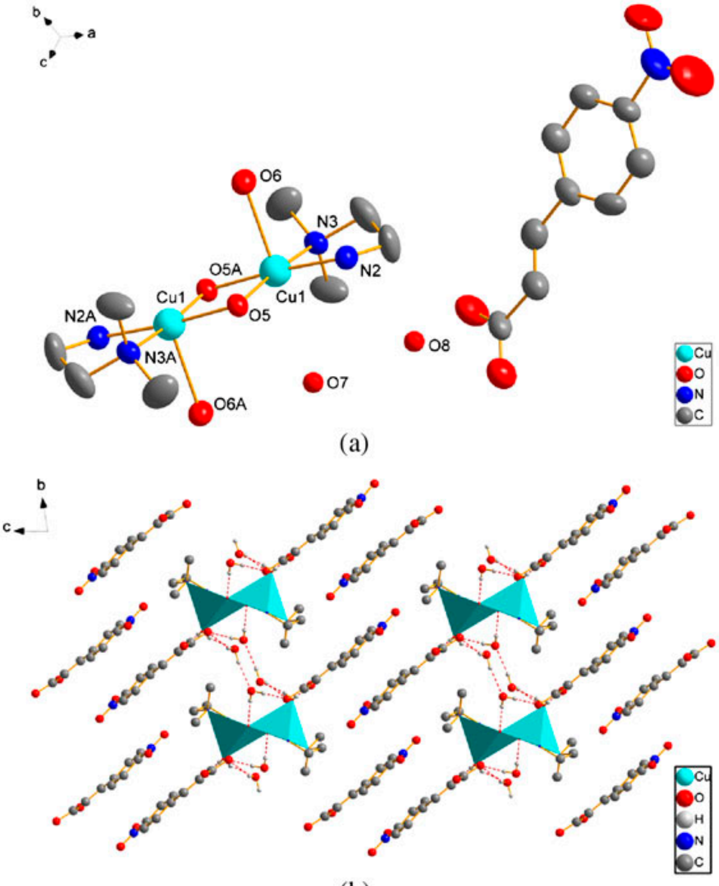
(a)

(b)

Figure 2. (a) Coordination environment of Ni in **2** drawn at 50% probability. All hydrogens are omitted for clarity. (b) The packing diagram of **2** along the *b*-axis with hydrogen bond interactions (colored in red) (see http://dx.doi.org/10.1080/00958972.2013.816417 for color version).

The bond distance between Cu and N2/N2A are both 2.0120(18) Å and the distance between Cu and N3/N3A are both 2.0117(19) Å, while the bond distance of Cu1–O5/O5A is 2.6392(16) Å.

Water is a bridge connecting different units. O6 (water) acts as bridging atom that connect O4 with O5. The hydrogen bonds consisted of these three oxygen atoms: O5–H···O4 (2.779(2) Å), O6–H···O4 ($-x$, $1-y$, $1/2+z$; 2.721(3) Å), and O6–H···O5 (x, $1-y$, $1/2+z$; 2.792(3) Å), while another H-bond is O5–H···O3 (x, $1+y$, z; 2.779(2) Å).



(a)

(b)

Figure 3. (a) Coordination environment of Cu in **3** drawn at 50% probability. All hydrogens are omitted for clarity. (b) The packing diagram of **3** along the *a*-axis with hydrogen bond interactions (colored in red) (see http://dx.doi.org/10.1080/00958972.2013.816417 for color version).

3.1.5. Description of 5. Crystal structure of **5** contains four independent mononuclear zinc(II) complexes in a unit cell (figure 5). The zinc(II) is tetrahedral, coordinated by two nitrogens and two oxygens. The average bond distances of Zn–N and Zn–O are 2.0345(3) and 1.9432(17) Å, respectively. The angles subtended at zinc(II) are 87.18(10)–123.00(6)°. There is a hydrogen bond between N4 (donor) and O2 (acceptor) from two different molecules with symmetry code ($2-x$, $1/2+y$, $-z$). After many refinement cycles, the U_{eq} of C11 still has a problem, suggesting two C11 in figure 5. This may be because 1,2-propanediamine is in a special position.

3.2. *Inhibitory activity against jack bean urease*

Transition metal ions as enzyme inhibitors exhibit different ability to inhibit urease, $Cu^{2+} > Ni^{2+} > Zn^{2+}$. This is in accord with inhibitory efficiency of metal ions towards

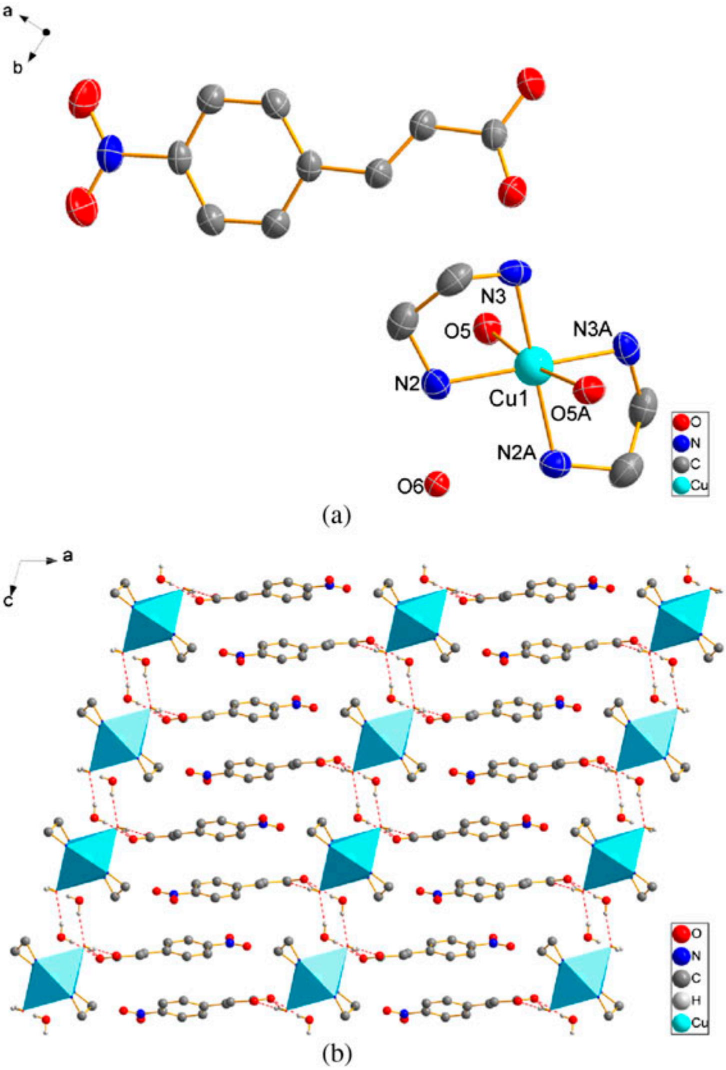
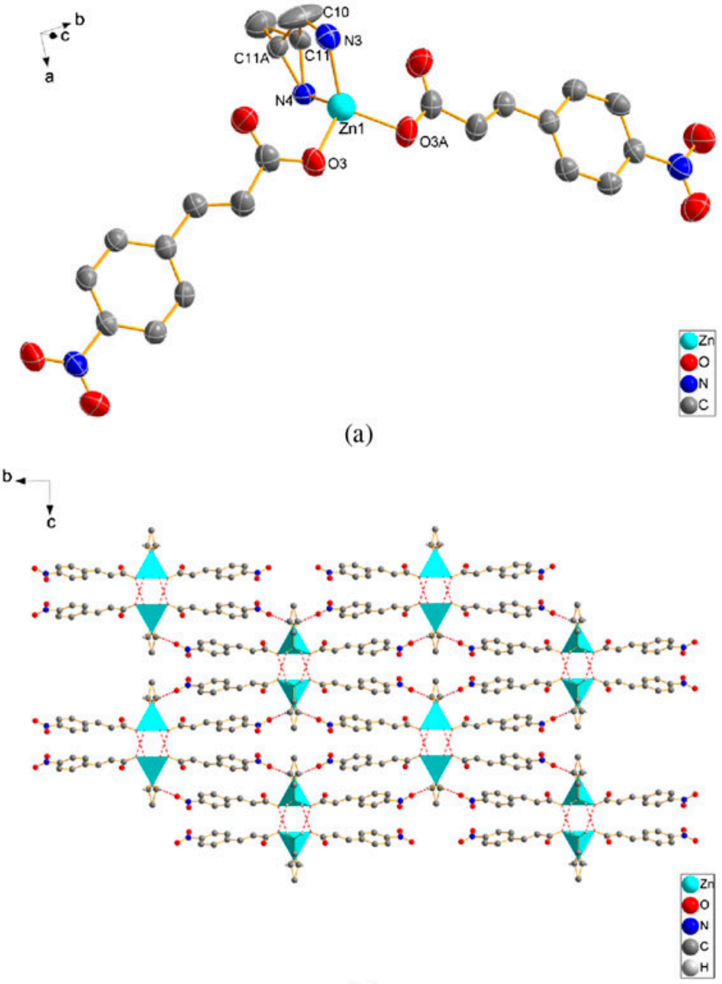


Figure 4. (a) Coordination environment of Cu in **4** drawn at 50% probability. All hydrogens are omitted for clarity. (b) The packing diagram of **4** along the *b*-axis with hydrogen bond interactions (colored in red) (see http://dx.doi.org/10.1080/00958972.2013.816417 for color version).

urease following the order: $Cu^{2+} > Ni^{2+} > Co^{2+} > Zn^{2+}$, which has been reported [25, 26]. Compared with other antiurease research ($IC_{50} = 0.95\ \mu M$, $1.2 \pm 0.1\ \mu M$ and $42.12\ \mu M$), **1**–**5** showed similar or even better activity against urease [27–30]. Compared with the standard inhibitor acetohydroxamic acid ($IC_{50} = 13.25\ \mu M$), 3-(4-nitrophenyl)acrylic acid ($IC_{50} = 17.09\ \mu M$) only has a weak influence on *jack bean* urease. Under the same conditions, **1**, **2,** and **5** ($IC_{50} = 10.09$, 10.44 and $13.10\ \mu M$) show better inhibition, while **3** and **4** showed potent urease inhibitory activities with IC_{50} value of 1.23 and $1.17\ \mu M$, respectively.



(a)

(b)

Figure 5. (a) Coordination environment of Zn in **5** drawn at 50% probability. All hydrogens are omitted for clarity. (b) The packing diagram of **5** along the *b*-axis with hydrogen bond interactions (colored in red) (see http://dx.doi.org/10.1080/00958972.2013.816417 for color version).

4. Conclusions

Five transition metal complexes were evaluated for inhibitory activity on *jack bean* urease. They all have inhibitory activity with copper(II) complexes **3** and **4** having the strongest activity ($IC_{50} = 1.23$ and 1.17 µM). This research showed new use of cinnamic acid and the activity data confirmed that transition metal complexes are potential inhibitors against urease.

Supplementary material

Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre (CCDC 923178–923182 for **1**–**5**). Copy of this information can be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: (+44) 1223-336033; E-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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