Original Article

Synthesis of Transition Metal Complexes of Isoniazid Derivatives and Urease Inhibition Activity Detection

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ABSTRACT

It have been reported that the transition metal complex of Schiff base ligands have the ability to inhibit urease. Herein, in this manuscript, two novel transition metal complexes $[Cd_2(L)_2\bullet(H_2O)]$ (1), [Pb(L)•, $[Pbe_2)$ were synthesized based on chelating hydrazone ligand *N*′-(pyridin-2-ylmethylene)isonicotinohydrazide (L). These compounds were tested by single crystal X-ray diffraction and determined by structure and tested for urease resistance *in vitro*. The complex 2 exhibited better the activities of inhibiting than the positive control acetohydroxamic acid with an IC_{50} = 2.5 μM, while the complex 1 showed weak activity, and complex 2 acted as an effective urease inhibitor.

Key words: Cadmium(II) complexes, Plumbum(II) complexes, Crystal structure, Schiff base, Urease inhibitor.

INTRODUCTION

Urease (EC 3.5.1.5; urea amidohydrolase) is a nickel structure enzyme belonging to the phosphotriesterase and superaminolysis families which is widespread in nature and promotes the production of carbon dioxide and ammonia from urea.[1,2] Excessive urease activity can lead to the continuous formation of sputum, which leads to increased permeability of the gastric mucosa. In addition, urease promotes the survival of *Helicobacter pylori* (*H. pylori*) in a low pH gastric environment and, when severe, leads to gastric cancer or peptic ulcer.[3,4] The continued release of ammonia can cause a variety of metabolic disorders and damage GIT epithelium through its interaction with the human immune system.[5] There are many ways to control urease activity. Urease inhibitors can be widely divided into acetohydroxamic acid, 1, 4 - benzoquinone, humic acid,[6,7] as well as other organic compounds and heavy metal ions like Cu^{2+}, Zn^{2+}, Pd2 + and Cd^{2+}.[8] However, available inhibitors are inefficient at present and the inhibitory activity of urease is still of great potential. Hence, it is highly desirable to obtain more and more urease inhibitors with good stability, high bioavailability and low toxicity.

Transition metal complexs combined with the schiff base ligands have been studied a lot in recent years because of their novel structures and potential applications in many aspects.[9-11] Schiff base metal complexes have also been reported to have the ability to inhibit urease. [4,12-15] Hereof, we accounted two new type of complexes with crystal structures of $[Cd_2(HL1)_2\cdot(H_2O)]$ (1) and [Pb(HL1)SCN] (2), the structure of complexes by using single crystal X-ray diffraction analysis. All the compounds obtained were tested for jack bean urease inhibitory activity *in vitro*.

MATERIALS AND METHODS

Materials and Instrumentation

Urease (given by jack beans, type III, activity of 31660 units/mg solids), HEPES buffer and urea (Molecular Biology Reagent) were provided by Sigma-Aldrich Co. (St. Louis, MO, USA). 2-Pyridinecarboxaldehyde was purchased from Aladdin and used without purification. All solvents and chemicals used

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in the synthesis require no further purification and they are reagent grade.

C, H, N element analysis were carried out on Perkin-Elmer 240C analyzer. The crystal date of Schiff base ligand and complexus 1, 2 were gathered on Bruker D8 VENTURE PHOTON diffractometer. The enzyme activity of inhibiting was determined on BioTek Synergy™ HT microplate reader.

General method for the preparation of the ligand and complexes

Synthesis of Schiff base ligand(L)

2-Pyridinecarboxaldehyde (2mmol, 0.19mL) was added to the solution of isonicotinohydrazide (2mmol, 0.2743 g) in methanol (20mL). Mixture in 30°C methanol refluxed for 1 hr.

Synthesis of complexes

Complex 1: A methanol and N,N-dimethylformamide (10 mL,1:1 v/v) 20 mL of Schiff base ligand L solution (0.1 mmol) was join the stir in methanol solution (5 mL) of $Cd(NO_3)_2 \cdot 4H_2O$ (0.05 mmol). Stirring the mixture at room temperature for 30 min and then filtered. After two days, the solution slowly evaporates in the air, forming single crystals of X-ray quality. Yield: 251 mg (56%). Anal. Calc. for C, 32.16; H, 2.36; N, 17.19. Found: C, 32.23; H, 2.38; N, 17.58 %.

Complex 2: A methanol and N,N-dimethylformamide (10 mL,1:1 v/v) 20 mL of Schiff base ligand L solution (0.1 mmol) was join the stir in methanol solution (5 mL) of $PbSO_4$ (0.05 mmol). Stirring the mixture at room temperature for 30 min and then filtered. After two days, the solution slowly evaporates in the air, forming single crystals of X-ray quality. Yield: 11 mg (45 %). Anal. Calc. for C, 30.70; H, 2.18; N, 13.77. Found: C, 30.58; H, 2.19; N, 14.10%.

Crystal structure determinations

For data collection, a single crystal matching the single crystal X-ray analysis is mounted on a glass fiber. The intensity data of complex **1** and complex **2** were then collected at 296K using graphite monochromatized Mo Kα radiation (zed Mo K at 296K using graphite ng the single crystal X-ray analysis is mounted SHELXL-97[16] program, and F2 was optimized by SHELXL-97 program which are improved by full matrix least squares technique.[17] All non-hydrogen atoms are anisotropic. All hydrogen atoms are geometrically fixed and allow for refinement using isotropic thermal parameters. Table 1 lists crystal data and a summary of structural refinements for the complexes.

Determination of urease inhibitory activity of Jack bean

The determination of urease activity was conducted according to Tanaka,[18] reports of the literature. The complex containing 25 μL (20 KU/L)(dissolved in distilled water) and 25 μL (dissolved in DMSO/H_2O mixture (1:1 V/V) in different concentrations was precultured for 1 h at 37°C in a 96-well plate. After incubation, joined with 500 mM of urea and 0.002% of phenol red pH 6.8 100 mM HEPES (N-[2-hydroxyethyl] piperazine-N'-[2-ethanesulfonic acid]) buffer 200 L, 37°C incubation. The reaction was measured by a microplate meter (570 nm), and sufficient ammonium carbonate was produced to raise the PH of HEPES buffer from 6.8 to 7.7, with the endpoint determined by the phenol red indicator color.

Supplementary Materials

Supplementary material has been deposited with the Cambridge Crystallographic Data Centre (nos. 1481821 (1) and 1481822 (2)); deposit@ccdc.cam.ac.uk or http://www.ccdc. cam. ac.uk).

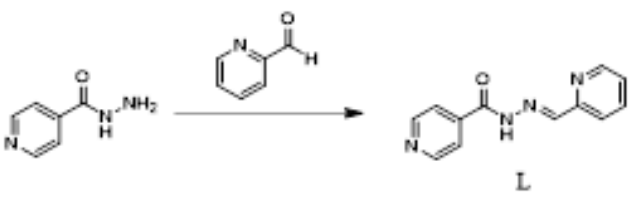
RESULTS AND DISCUSSION

General preparation methods of ligands and complexes

Synthetic route of the Schiff base (L) were shown in Scheme 1. Schiff base (L) was reacted by 2-Pyridinecarboxaldehyde and isonicotinohydrazide in the ratio of 1:1. Finally, the Schiff base and metal ($Cd(NO_3)2nal_2O$ and $PbSO_4$) reacted in the ratio of 2:1 separately to get the complexes 1 and 2. Crystals of complexus 1 and 2 fited for X-ray diffraction can be separated from methanol or DMF/methanol after slow evaporation of the organic solvent for about a week. Metal complexes 1 and 2 of crystallography data showed in Table 1.

Specific description of crystal structure

Figures 1-6 shows the molecular structures of complexes 1 and 2 determined by single crystal X-ray analysis. Their phase key distances and angles are shown in Tables 2 and 3.



Scheme 1. Synthetic route of Ligand L

Table 1: Crystal data for complexes 1, 2.

Complexes	1	2
Empirica Formula	$C_{24}H_{19}Cd_2N_{11}O_{12}\cdot H_2O$	$C_{13}H_{11}N_5O_2PbS$
Formula Weight	896.34	508.54
Crystal System	monoclinic	monoclinic
Space group	$P2_1$	$P2_{1/n}$
a(Å)	7.9194(3)	7.1906(5)
b(Å)	14.9823(6)	16.4328(11)
c(Å)	13.4384(6)	12.5192(9)
α(°)	90	90
β(°)	99.123(1)	92.549(2)
γ(°)	90	90
T(K)	273	273
V(Å^3)	1574.31(11)	1477.83(18)
Z	2	4
D_c(gcm^{-3})	1.891	2.286
F(000)	884	952
μ(Mo-Kα) (mm^{-1})	1.434	11.571
Theta min/max	2.0/27.5	3.0/25.5
Unique	[$R_{(int)}$= 0.027] 0.0732,0.2433	[$R_{(int)}$= 0.045]
Final R_1, ωR_2 [I > 2σ(I)]	0.0325, 0.0628	0.0466, 0.1224
R indices (all data)	R_1 = 0.0427	R1 = 0.0558
	wR_2 = 0.0662	wR_2 = 0.1303
Goodness of fit on F^2	1.022	1.100

Table 2: Selected bond lengths (Å) for complexes 1, 2.

1		2
Cd(1)-O(1) 2.522(3)	Cd(2)-O(4) 2.631(4)	Pb(1)-S(1) 2.893(4)
Cd(1)-O(6) 2.538(4)	Cd(2)-O(12) 2.361(3)	Pb(1)-O(1) 2.366(7)
Cd(1)-O(7) 2.393(4)	Cd(2)-N(4) 2.339(4)	Pb(1)-O(2) 2.636(9)
Cd(1)-O(9) 2.358(3)	Cd(2)-N(6) 2.306(4)	Pb(1)-N(2) 2.674(8)
Cd(1)-O(10) 2.523(3)	Cd(2)-N(7) 2.463(4)	Pb(1)-N(3) 2.468(9)
Cd(1)-N(1) 2.426(4)	Cd(2)-O(2) 2.358(3)	Pb(1)-N(1)b 2.819(10)
Cd(1)-N(2) 2.373(4)	Cd(2)-O(3) 2.386(3)	
Cd(1)-N(9) 2.316(4)		

Table 3: Selected angles (°) for complexes 1, 2.

1		2
O(1)-Cd(1)-O(6) 131.48(10)	O(10)-Cd(1)-N(9) 82.71(13)	S(1)-Pb(1)-O(1) 86.1(2)
O(1)-Cd(1)-O(7) 82.04(12)	N(1)-Cd(1)-N(2) 67.30(12)	S(1)-Pb(1)-O(2) 157.5(2)
O(1)-Cd(1)-O(9) 85.75(10)	N(1)-Cd(1)-N(9) 143.56(14)	S(1)-Pb(1)-N(2) 85.1(2)
O(1)-Cd(1)-O(10) 133.39(10)	N(2)-Cd(1)-N(9) 145.37(12)	S(1)-Pb(1)-N(3) 83.8(2)
O(1)-Cd(1)-N(1) 131.26(12)	O(2)-Cd(2)-O(3) 88.24(13)	S(1)-Pb(1)-N(1)b 77.7(2)
O(1)-Cd(1)-N(2) 64.30(10)	O(2)-Cd(2)-O(4) 129.71(12)	O(1)-Pb(1)-O(2) 76.0(3)
O(1)-Cd(1)-N(9) 84.47(12)	O(2)-Cd(2)-O(12) 99.21(10)	O(1)-Pb(1)-N(2) 127.6(3)
O(6)-Cd(1)-O(7) 51.33(13)	O(2)-Cd(2)-N(4) 83.98(12)	O(1)-Pb(1)-N(3) 64.5(3)
O(6)-Cd(1)-O(9) 140.64(11)	O(2)-Cd(2)-N(6) 67.12(13)	O(1)-Pb(1)-N(1)b 75.1(3)
O(6)-Cd(1)-O(10) 88.45(11)	O(2)-Cd(2)-N(7) 135.94(12)	O(2)-Pb(1)-N(2) 95.0(3)
O(6)-Cd(1)-N(1) 72.87(12)	O(3)-Cd(2)-O(4) 49.87(13)	O(2)-Pb(1)-N(3) 76.3(3)
O(6)-Cd(1)-N(2) 111.91(12)	O(3)-Cd(2)-O(12) 171.91(13)	O(2)-Pb(1)-N(1)b 110.0(3)
O(6)-Cd(1)-N(9) 77.06(12)	O(3)-Cd(2)-N(4) 100.08(13)	N(2)-Pb(1)-N(3) 63.2(3)
O(7)-Cd(1)-O(9) 167.76(12)	O(3)-Cd(2)-N(6) 91.52(13)	N(2)-Pb(1)-N(1)b 150.7(3)
O(7)-Cd(1)-O(10) 139.19(11)	O(3)-Cd(2)-N(7) 87.96(14)	N(3)-Pb(1)-N(1)b 136.4(3)
O(7)-Cd(1)-N(1) 94.93(14)	O(4)-Cd(2)-O(12) 125.01(11)	
O(7)-Cd(1)-N(2) 79.62(13)	O(4)-Cd(2)-N(4) 78.84(13)	
O(7)-Cd(1)-N(9) 81.68(13)	O(4)-Cd(2)-N(6) 129.10(13)	
O(9)-Cd(1)-O(10) 52.30(9)	O(4)-Cd(2)-N(7) 76.77(13)	
O(9)-Cd(1)-N(1) 92.54(12)	O(12)-Cd(2)-N(4) 83.94(11)	
O(9)-Cd(1)-N(2) 94.41(11)	O(12)-Cd(2)-N(6) 88.52(11)	
O(9)-Cd(1)-N(9) 97.95(11)	N(4)-Cd(2)-N(7) 139.79(14)	
O(10)-Cd(1)-N(1) 76.43(13)	N(6)-Cd(2)-N(7) 69.13(14)	
O(10)-Cd(1)-N(2) 129.35(11)	N(4)-Cd(2)-N(6) 148.53(15)	
O(12)-Cd(2)-N(7) 84.50(12)		

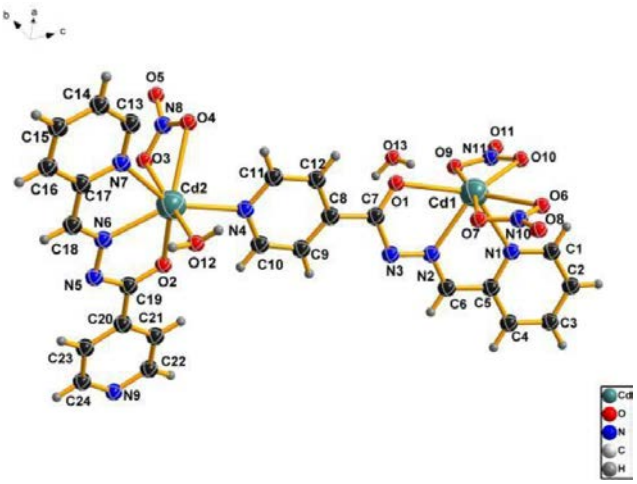


Figure 1: Crystal structure of complex 1. Displacement ellipsoids are shown at the 50% probability level.

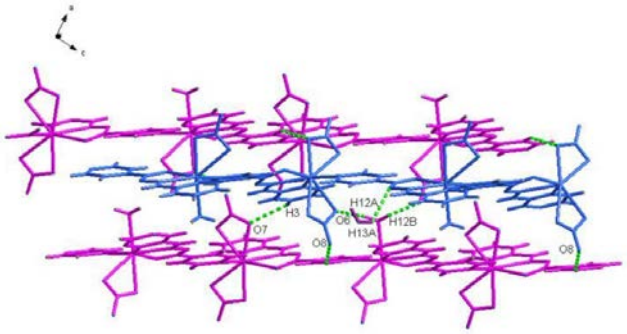


Figure 2: View of the two-dimensional supramolecular sheet of complex 1.

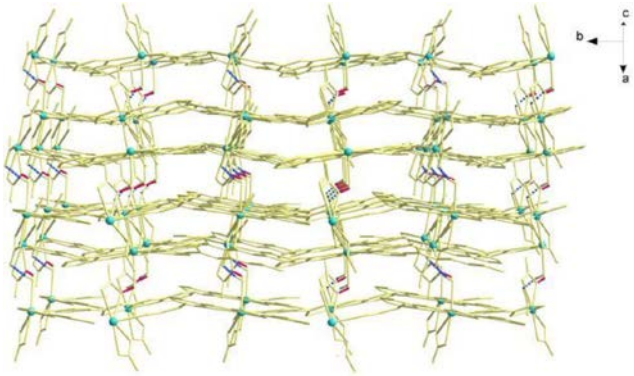


Figure 3: View of the three-dimensional supramolecular sheet of complex 1.

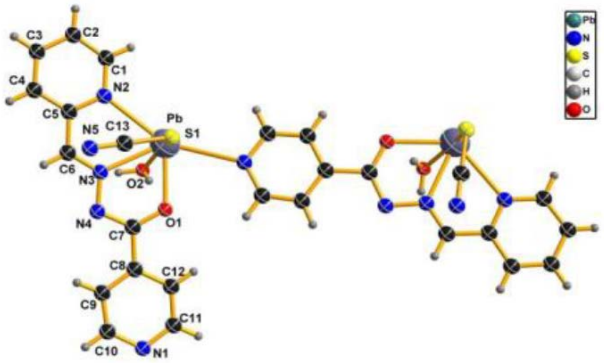


Figure 4: Crystal structure of complex 2.

Crystal structure of target complex 1

X-ray crystal analysis showed that the molecular structure of target Complex 1 (CCDC:1481821) grown in the monoclinic system $P2_1$ space series. In the asymmetric unit of 1 (shown in Figure 1), each Cd atom in the compound is derived from the NNO donor of Schiff base ligand, forming slightly distorted square-planar geometry. Interestingly, one Cd atom is harmonized with four O atoms given by two NO_3^-, another Cd atom is harmonized with two O atoms given by the NO_3^- with a water molecule. Table 3 shows the hydrogen bonds of complex 1,where adjacent molecules are stacked in parallel. A variety of hydrogen bonding interactions occur between adjacent molecules in complex 1, wherein O-H...O type includes O(12)-H(12A)...O(6)^{I} [symmetric code:I: -x,1/2+y,2-z], O(12)-H(12B)...O(5)^{II} [symmetric code:II: -1+x,y,z]; C-H...O type includes C(3) -H(3)...O(7)^{IV} [symmetric code:IV: -x,-1/2+y,1-z], C(9)-H(9)...O(3)^{V} [symmetric code:V:-x,-1/2+y,2-z], C(11)-H(11)...O(8)^{VI} [symmetric code:VI: :-x,1/2+y,2-z], C(23)-H(23)...O(9)^{VII} [symmetric code:VII: 2-x,1-y,1-z]. In addition, N5 of complex 1 forms O(13)-H(13A)...N(5)^{III}[symmetric code:III: -x,-1/2+y,1-z] with free water molecules, (exhibited in Figure 2). The crystal structure is also steady by O(12)-H(12A)...O(6)^{I} [symmetric code: I:-x, 1/2 y, 2-z]hydrogen bonds , connecting the 2D network to a 3D The internet, (exhibited in Figure 3).

Crystal structure of target complex 2

X-ray crystal analysis showed that the molecular structure of target complex 2 (CCDC:1481822) grown in the monoclinic $P2_{1/n}$ space series. As shown in Figure 4, it resemble the crystal structure of complex 1, each Pb atom in the complex is harmonized with the NO donor of Schiff base ligand, forming slightly distorted square-planar geometry. Hydrogen bonds for complexes 1 and 2 are presented in Table 4. Separately, two Pb atoms are both coordinated by one O atom from water. As indicated in Figure 5, the two-dimensional network supramolecular structure arises from the formation of complex 2 along the plane of BC. The hydrogen bonds between nitrogen atoms from the coordinated water

Table 4: Hydrogen bonds for complexes 1, 2 [Å].					
Complex	**D-H•••A**	**d(D-H)**	**D(H...A)**	**d(D...A)**	**d(D-H...A)**
1	O(12)-H(12A)•••O(6)^{I}	0.85	1.90	2.717(5)	161
	O(12)-H(12B)•••O(5)^{II}	0.84	2.10	2.892(5)	159
	O(13) -H(13A)•••N(5)^{III}	0.85	2.41	2.940(6)	122
	C(3) -H(3)•••O(7)^{IV}	0.93	2.51	3.142(7)	125
	C(9)-H(9)•••O(3)^{V}	0.93	2.51	3.393(6)	159
	C(11)-H(11)•••O(8)^{VI}	0.93	2.40	3.183(7)	141
	C(23)-H(23)•••O(9)^{VII}	0.93	2.57	3.431(5)	154
2	O(2)-H(2B)•••N(4)^{VIII}	0.85	2.08	2.892(13)	159

Symmetry code: I: -x,1/2+y,2-z; II: -1+x,y,z;III:-x,-1/2+y,1-z; IV:-x,-1/2+y,1-z; V:-x,-1/2+y,2-z; VI:-x,1/2+y,2-z;VII:-x,1/2+y,1-z;VII:2-x,1-y,1-z.

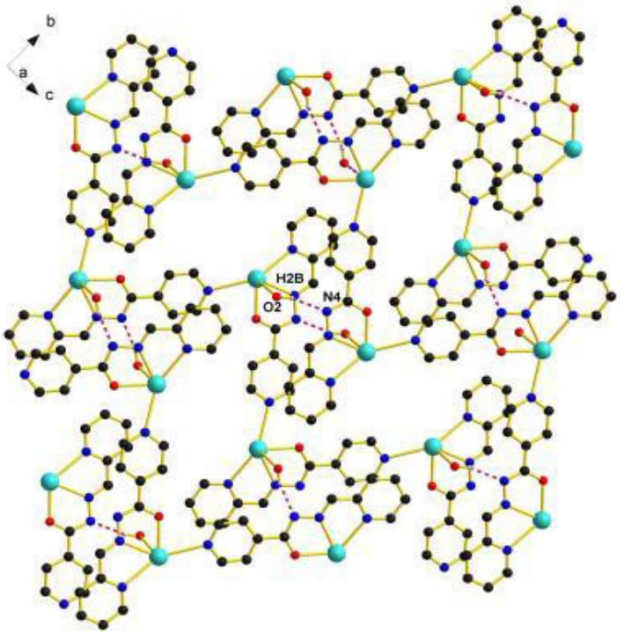


Figure 5: View of the two-dimensional supramolecular sheet of complex 2.

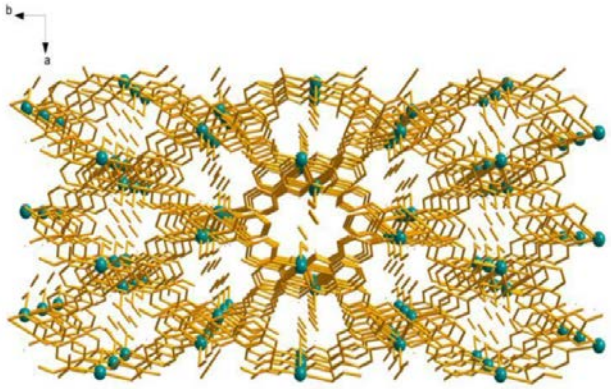


Figure 6: View of the three-dimensional supramolecular sheet of complex 2.

Table 5: Inhibition of jack bean urease by complexes 1, 2.	
Tested materials	**IC_{50} ±SD (μM)**
1	62.3 ± 4.7
2	2.5 ± 0.3
L	> 100
Acetohydroxamic acid	33.5 ± 4.6

and the Schiff base ligand form a O(2)-H(2B)...N(4)^{III} [symmetry code: III:2-x,1-y,1-z] hydrogen-bonding interreaction, giving into the construction of a 2D supramolecular plate. The 3D framework of 2 about hydrogen bonds is presented in Figure 6.

Inhibitory activity against jack bean urease

The ability of the three new transition-metal complexus with Schiff base ligands inhibiting jack bean urease was screened in this work (Table 5). To compare with the acetohydroxamic acid (AHA,a reversible inhibitor, IC_{50} = 33.5 μM), the synthetic ligands doesn't have the ability to inhibit jack bean urease, and complex 1 to jack bean urease displayed a strong inhibitory activity. Complex 2 exhibited a weak ability to inhibit the jack bean urease. It is important to note that the complexes studied form an order in terms of inhibition intensity of jack bean urease: 2 > 1, with IC_{50} 2.5, 62.3 μM, severally. It is generally believed that heavy metal ions inhibit urease by binding to the sulfhydryl groups of cysteines and possibly to the nitrogen -(histidine) and oxygen -(aspartate and glutamate) at the active site of urease. The results show that the inhibitory activity of schiff alkali metal complexes as urease inhibitors depends not only on the organic ligands but also on the central ions.

CONCLUSION

In summary, a novel Schiff base ligand transition metal complex containing an isoniazid structure is described in this article. The crystal structure and urease inhibition activity of the two kinds of complexes were examined. As shown in Table 5, Complex 2 showed the most effective urease inhibition activity to aim at jack bean urease, with an IC_{50} value of 2.5 μM, which could be further developed as a novel urease inhibitor.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

Cr: Chromium; **Pb:** Plumbum; ***H. pylori:*** *Helicobacter pylori*; **DMSO:** Dimethyl Sulfoxide; **HEPES**: 2-[4-(2-Hydroxyethyl)-1-piperazinyl]ethanesulfonic acid; **AHA:** Acetohydroxamic acid.

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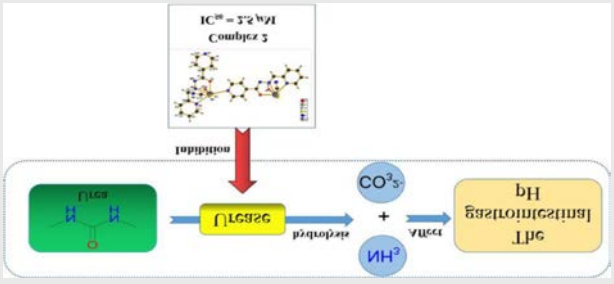
PICTORIAL ABSTRACT



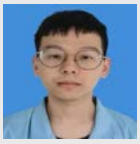
SUMMARY

The complex 2 exhibited better the activities of inhibiting than the positive control acetohydroxamic acid with an IC_{50} = 2.5 μM, acted as an effective urease inhibitor.

About Authors

Yi-Heng Zhang, Master Candidate. The research interests include the design, synthesis and bioactivity evaluation of small molecule inhibitors of natural product kinase. Design and development of antitumor lead drugs.

Juan Sun, Phd, Associate Professor. Currently engaged in the design, synthesis and biological activity evaluation of natural products, as well as anti-tumor, anti-inflammatory and anti-bacterial drug design and development.



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