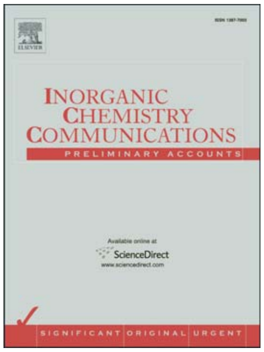


Crystal structures and biological activities of Mn (II) and Cd (II) complexes from an asymmetrical Schiff base ligand

Jing-An Zhang, Yu Li, Yan-Zhong Fan, Xun-Zhong Zou, Ya-Jie Liu, Li-Jie Zhang, Sheng-Run Zheng

PII: S1387-7003(14)00420-1
DOI: doi: 10.1016/j.inoche.2014.09.030
Reference: INOCHE 5753

To appear in: *Inorganic Chemistry Communications*

Received date: 22 July 2014
Revised date: 17 September 2014
Accepted date: 22 September 2014

Please cite this article as: Jing-An Zhang, Yu Li, Yan-Zhong Fan, Xun-Zhong Zou, Ya-Jie Liu, Li-Jie Zhang, Sheng-Run Zheng, Crystal structures and biological activities of Mn (II) and Cd (II) complexes from an asymmetrical Schiff base ligand, *Inorganic Chemistry Communications* (2014), doi: 10.1016/j.inoche.2014.09.030

Title Page

Crystal structures and biological activities of Mn (II) and Cd (II) complexes from an asymmetrical Schiff base ligand

Jing-An Zhang [a, *], Yu Li [b, †, *], Yan-Zhong Fan [c], Xun-Zhong Zou [a], Ya-Jie Liu [a], Li-Jie Zhang [a], Sheng-Run Zheng [d]

[a] School of Pharmacy and College of Traditional Chinese Medicine, Guangdong Pharmaceutical University, Guangzhou 510006, P. R. China. zhangja@126.com
[b] Department of Environmental Engineering, Guangdong Industry Technical College, Guangzhou 510300, P. R. China. liyuletter@163.com
[c] Chemistry and Chemical Engineering College, Sun Yat-Sen University, Guangzhou 510275, P. R. China
[d] School of Chemistry and Environment, South China Normal University, Guangzhou, 510006, P. R. China

† Author information. These authors contributed equally to this work. Jing-An Zhang and Yu Li.

***** Corresponding author.

******Corresponding author. Tel: +86 20 39352141. E-mail: zhangja@126.com (J. A. Zhang); liyuletter@163.com (Y. Li)

Crystal structures and biological activities of Mn (II) and Cd (II) complexes from an asymmetrical Schiff base ligand

Jing-An Zhang [a, *], Yu Li [b, †, *], Yan-Zhong Fan [c], Xun-Zhong Zou [a], Ya-Jie Liu [a], Li-Jie Zhang [a], Sheng-Run Zheng [d]

[a] School of Pharmacy and College of Traditional Chinese Medicine, Guangdong Pharmaceutical University, Guangzhou 510006, P. R. China. zhangja@126.com

[b] Department of Environmental Engineering, Guangdong Industry Technical College, Guangzhou 510300, P. R. China. liyuletter@163.com

[c] School of Chemistry and Chemical Engineering, Sun Yat-Sen University, Guangzhou 510275, China.

[d] School of Chemistry and Environment, South China Normal University, Guangzhou, 510006, P. R. China

Abstract: The Mn(II) and Cd(II) complexes of an asymmetrical Schiff base ligand 4-(1*H*-benzimidazol-2-yl)-phenyl]-pyridin-4-methyl amine have been prepared by the method of diethyl ether diffusion. The structures of the complexes were identified by elemental analysis (EA), infrared spectra (IR) and single-crystal X-ray diffraction. It was revealed that complexes **1** and **2** were composed of discrete mononuclear structures**,** and formed schistose structures via two different kinds of hydrogen bonds. The antibacterial and antifungal activities of the ligand and two complexes were tested, which may provide useful information for the research and application in pharmaceutical chemicals.

Keywords: Crystal structures; Antibacterial and Antifungal Activities; [4-(1*H*-benzimidazol-2-yl)-phenyl]-pyridin-4-methyl amine; Schiff base

In the past few decades, the Schiff base ligand and its complexes containing benzimidazolyl and pyridinyl terminal groups have attracted more and more attention in the application of gas storage and separation[1], photoluminescent sensors and devices [2], checkpoint kinase inhibitors [3], and other functional materials [4-6]. Reports on the bioactivities of complexes from Schiff base ligands such as antimicrobial, antifungal, antiviral, antitumor and cytotoxic activities have also aroused great interest in recent years [7-13].

Recently, Wu and Xia have reported a series of transition metal complexes containing symmetrical benzimidazolyl and pyridinyl terminal groups [14-15]. In order to investigate the coordination behavior of asymmetrical Schiff base ligand containing benzimidazolyl and pyridinyl groups, we herein designed a rigid ligand, [4-(1*H*-benzimidazol-2-yl)-phenyl]-pyridin-4-methylamine (L) (Figure **1**). Syntheses and structures of the ligand and its Mn/Cd (II) complexes were reported here. The antibacterial and antifungal activities of the ligand and its two complexes were also tested, which may provide useful information for the research and application of pharmaceutical chemicals.

The ligand [4-(1*H*-benzimidazol-2-yl)-phenyl]-pyridin-4-methylamine (L) was prepared from the reaction of 4-(2-benzimidazolyl) aniline [16-17] and 4-pyridine formaldehyde catalyzed by formic acid and anhydrous ethanol as solvent, and single crystals of Mn/Cd(II) complexes were obtained from diffusion of diethyl ether into the mixture of the ligand and Mn/Cd(II) salts in methanol, dichloromethane and acetonitrile solvents [17].

<Insert Figure **1** here>

The crystallographic data and structure refinement summary for complexes **1** and **2** are listed in Table S1. The **s**elected Bond lengths [Å] and angles [°] for **1** and **2** were presented in Table S2 and S3.

Single-crystal diffraction analyses revealed that the basic coordination units of complexes **1** and **2** are similar; both of which are discrete mononuclear complexes composed of one metal and two ligands. In complex **1**, the asymmetry unit contains a half of Mn (II) ion, one L, one CH_3OH molecule and one Cl^- anion. The Mn (II) center is six-coordinated by two pyridine N atoms (Mn(1)-N(1) = 2.276 (3) Å) from two different ligands, two O atoms from two CH_3OH molecules (Mn (1)-O (1) = 2.231 (2) Å), and two Cl^- anions (Mn (1)-Cl (2) = 2.4910 (8) Å) (Figure **2**a). The ligand is coordinated to Mn(II) by its pyridine N atom, whereas the benzimidazole N atom remain uncoordinated, which may be due to steric hindrance enhanced by the benzene ring on the 2-position of benzimidazole group. However, the N and -NH on benzimidazole ring can act as strong hydrogen bonding acceptor and donor respectively and extend the mononuclear unit into higher dimensional supramolecular network.

There are two kinds of hydrogen bonds in complex **1.** O-H···N hydrogen bond is formed between CH_3OH molecule and the tertiary N atom on benzimidazole ring (O(1)–H(1) ···N(3), H···O 2.020 Å, O···N 2.754 Å, ∠OHN 133^o), and N-H···Cl hydrogen bond is formed between the secondary -NH on benzimidazole ring and the Cl^- anion (N(4)–H(4) ···Cl(2), H···O 2.301 Å, N···Cl 3.177 Å, ∠NHCl 173.81^o) (Figure **2**b). Such hydrogen bonds link the basic units into a 2D hydrogen-bonding layer, which extends along (1 0 -2) plane (Figure **2**c). The 2D layers pack into a 3D framework in *abab* mode.

<Insert Figure **2** here>

The asymmetry unit of complex **2** contains a half of Cd (II) ion, one L, two Ac^- anions, one coordinated and three uncoordinated water molecules. The biggest difference between complexes **1** and **2** is the coordination geometry of metal center and the coordinated solvent molecules and anions. As shown in Figure **3**a, the Cd (II) ion in complex **2** is seven-coordinated by four acetate O atoms and one water O atom in the equatorial plane and two pyridine N atoms from two different ligands on axial sites, which can be described as a distorted pentagonal bipyramid geometry.

The coordination mode of L in **2** is the same as that in **1**. The resulting mononuclear basic unit contains lots of hydrogen bonding sites, in which the -NH on benzimidazole and the coordinated water molecule act as hydrogen bonding donors, and the N on benzimidazole and acetate O atoms act as hydrogen bonding acceptors. Therefore, such basic units could form higher dimensional network via hydrogen bonding between them. There are two kinds of hydrogen bonds, N-H···O hydrogen bond between the NH group of benzimidazole and the oxygen of the acetate anion [N(2)–H(2A) ···O(1), H···O 1.888 Å, N···O 2.765 Å, ∠NHO 173.56^o] and O-H···N hydrogen bond between the coordinated water and the tertiary nitrogen atom on benzimidazole ring [O(1w)–H(1wb) ···N(1), H···O 1.921 Å, O···N 2.757 Å, ∠OHN 166.74^o], which connect the mononuclear units into a 2D layer (Figures **3**b and **3**c). The 2D layers extend in *ab* plane and pack along *c* direction in *abcdabcd* mode, give rise to a 3D supramolecular framework. Small channels are formed in *b* direction and occupied by uncoordinated water molecules (Figure S1).

<Insert Figure **3** here>

Large voids are formed during the crystal packing in complex **1** and **2**, both generating 23% solvent accessible space in lattice (Figure **4**), suggesting that they can be regarded as porous material and have the potential ability to adsorb gases or other guests such as small organic molecules in solution or solid state [21].

<Insert Figure **4** here>

From the antibacterial results listed in Table **1**, we can see that the ligand and its complexes have different inhibition activities against various kinds of bacteria. The ligand L has definite efficiency in inhibiting *S. aureus* (MIC value was 25μg/mL), and weak against *E. coli, P. aeruginosa* and *S. ureae* (MIC values were over 128μg/mL). While complexes **1** and **2** show good antibacterial activities against both the gram-positive bacteria (*S. aureus* and *S. ureae*) and the gram-negative bacteria (*P. aeruginosa* and *E. coli*) (MIC values were over 50 μg/mL). Specifically, complex **1** shows better activities against *E. coli* (MIC value was 3.125 μg/mL) than the other bacteria; while complex **2** shows better activities against *P. aeruginosa* (MIC value was 1.56 μg/mL) than the other bacteria. Both of them show potential applications in broad spectrum anti-bacteria field.

The antifungal activities of the ligand and its two complexes are in-effective against the three kinds of fungals tested here (MIC > 125 μg/mL). The detailed experimental results are listed in Table **1**.

<Insert Table **1** here>

In conclusion, Mn (II) and Cd (II) complexes based on an asymmetrical Schiff base ligand were prepared and characterized. The complexes are comprised of discrete mononuclear structure and are further connected by hydrogen bonds into two different supramolecular frameworks. Antibacterial activity tests show that the ligand has definite efficiency in inhibiting *S. aureus* and the two complexes are good at inhibiting the gram-positive and gram-negative bacteria.

Acknowledgement

The authors gratefully acknowledge Guangdong Province Universities and Colleges High Level Talent Project (2011QY01), Science and Technology Planning Project of Guangdong Province (2012A020603023), the Natural Science Foundation of Guangdong Industry Technical College (KJ201301) for financial support.

Appendix A. Supplementary material

Supplementary data to this article can be found online at http://

References

[1] Q. Wang, R. Yang, C. F. Zhuang, J. Y. Zhang, B. S. Kang, C. Y. Su. Guest-Inclusion Behavior of Double-Strand 1D Coordination Polymers Based on N, N’-Type Schiff Base Ligands. Eur. J. Inorg. Chem. (2008) 1702–1711.

[2] C. Qin, X. L. Wang, E. B. Wang, L. Xu. Layered zinc (II) and cadmium (II) dicarboxylates with aromatic chelate ligand-syntheses, crystal structures and luminescent properties. J. Mol. Str. 738 (2005) 91–98.

[3] K. L. Arienti, A. Brunmark, F. U. Axe, K. McClure, A. Lee, J. Blevitt, D. K. Neff, L. M. Huang, S. Crawford, C. R. Pandit, L. Karlsson, J. G. Breitenbucher. Checkpoint kinase inhibitors: SAR and radioprotective properties of a series of 2-arylbenzimidazoles. J. Med. Chem. 48(2005) 1873-1885.

[4] M. X. Tan, B. Liu, Y. C. Liu, Z. F. Chen, Z. Y. Zhou, H. Liang. Crystal structures of Schiff base from 4-aminoantipyrine and pyridine-4-carboxaldehyde and its perchlorate. Chin. J. Str. Chem. 27(12) (2008)

1506-1510.

[5] (a) C. Piguet, G. Bernardinelli, A. F. Williams. Preparation and crystal structure of the unusual double-helical copper (I) complex bis (2, 6-bis (1-methylbenzimidazol-2-yl) pyridine) dicopper (I) naphthalene-1, 5-disulfonate. Inorg. Chem. 28 (15) (1989)2920–2925. (b) A. Mukherjee, A. Dutta, A. D. Jana, G. K. Patra. Copper (I) and silver (I) coordination assemblies of imino-pyridyl and azino-pyridyl ligands: Syntheses, crystal structures, spectroscopic and photophysical properties. Inorg. Chim. Acta 404 (2013) 131–143.

[6] (a) T. D. Pasatoiu, J. P. Sutter, A. M. Madalan, F. Z. C. Fellah, C. Duhayon, M. Andruh. Preparation, crystal structures, and magnetic features for a series of dinuclear [$Ni^{II}Ln^{III}$] Schiff-base complexes: Evidence for slow relaxation of the magnetization for the Dy^{III} derivative. Inorg. Chem. 50(13) (2011)5890–5898. (b) C. R. Bhattacharjee, P. Goswami, H. A. R. Pramanik, P. C. Paul, P. Mondal. Reactivity of tris (acetylacetonato) iron (III) with tridentate [ONO] donor Schiff base as an access to newer mixed-ligand iron (III) complexes. Spectrochim. Acta Part A: Mol. Biomol. Spectro. 78(5) (2011)1408–1415. (c) C. R. Bhattacharjee, P. Goswami, P. Mondal. Synthesis, reactivity, thermal, electrochemical and magnetic studies on iron (III) complexes of tetradentate Schiff base ligands. Inorg. Chim. Acta 387 (2012)86–92.

[7] (a) B. Shaabani, A. A. Khandar, M. Dusek, M. Pojarova, F. Mahmoudi, A. Feher, M. Kajňaková. Two coordination polymers based on semicarbazone Schiff base and azide: synthesis, crystal structure, electrochemistry, magnetic properties and biological activity. J. Coord. Chem. 66(5) (2013) 748-762. (b) B. Shaabani, A. A. Khandar, F. Mahmoudi, M. A. Maestro, S. S. Balula, L. Cunha-Silva. Novel binuclear Cu (II) complexes combining a semicarbazone Schiff base with distinct bridging ligands: Structure and antimicrobial activity. Polyhedron 57 (2013)118-126.

[8] (a) R. K. Dubey, U. K. Dubey, C. M. Mishra. Synthesis, spectroscopic (IR, electronic and FAB-mass) and magnetic studies of some mixed ligand complexes of chromium (III). Indian J. Chem., Sectn A: Inorg., Bio-inorg., Physical, Theoretical & Anal. Chem. 45A (7) (2006)1638-1642. (b) R. K. Dubey, U. K. Dubey, S. K. Mishra. Synthesis, spectroscopic (IR, electronic, FAB-mass, and PXRD), magnetic, and antimicrobial studies of new iron (III) complexes containing Schiff bases and substituted benzoxazole ligands. J. Coord. Chem. 64(13) (2011) 2292-2301.

[9] S. Kumar, D. N. Dhar, P. N. Saxena. Application of metal complexes of Schiff bases-a review. J. Sci. & Indust. Res. 68(2009)181-187.

[10] S. Singh, H. Ojha, A. K. Tiwari, N. Kumar, B. Singh, A. K. Mishra. Design, synthesis, and in vitro antiproliferative activity of benzimidazole analogues for radiopharmaceutical efficacy. Cancer Biotherapy & Radiopharm. 25(2) (2010)245-250.

[11] N. Raman, S. J. Raja, A. Sakthivel. Transition metal complexes with Schiff-base ligands: 4-aminoantipyrine based derivatives–a review. J. Coord. Chem. 62(5) (2009) 691-709.

[12] M. Hranjec, K. Starčević, S. K. Pavelić, P. Lučin, K. Pavelić, G. K. Zamola. Synthesis, spectroscopic characterization and antiproliferative evaluation in vitro of novel Schiff bases related to benzimidazoles. Eur. J. Med. Chem. 46(6) (2011) 2274-2279.

[13] Y. Li, J. A. Zhang, Y. B. Wang, M. Pan, C. Y. Su. Crystal structures, DFT calculations and biological activities of three mercury complexes from a pentadentate thioether ligand. Inorg. Chem. Comm. 34 (2013) 4-7.

[14] H. L. Wu, X. C. Huang, B. Liu, F. Kou, F. Jia, J. K. Yuan, Y. Bai. Copper (II) complex based on a V-shaped ligand, 2, 6-*bis* (2-benzimidazolyl) pyridine: synthesis, crystal structure, DNA-binding properties, and antioxidant activities. J. Coord. Chem. 64(24) (2011) 4383-4396.

[15] Y. M. Xia, J. You, F. K. Yang. Synthesis of 1, 2-bisubstituted benzimidazole: 1, 3-Shift mechanism catalyzed by acid or base. J. Heterocyclic Chem. 48(1) (2011) 230–236.

[16] H. Liu, H. Q. Miao. Aryl-1, 3-azole derivatives and methods for inhibiting heparanase activity. WO 2005030206, 2005-04-07.

[17] (a) W. Pan, H. Q. Miao, Y. J. Xu, E. C. Navarro, J. R. Tonra, E. Corcoran, A. K. Lahiji, P., K. S. Alexander, W. C. Wong, H. Liu. 1-[4-(1H-Benzimidazol-2-yl)-phenyl]-3-[4-(1H-benzimidazol-2-yl)-phenyl]-urea derivatives as small molecule heparanase inhibitors. Bioorg. Med. Chem. Letters, 16 (2006) 409-412. (b) J. A. Zhang, M. Pan, J. J. Jiang, Z. G. She, Z. J. Fan, C. Y. Su. Syntheses, crystal structures and antimicrobial activities of thioether ligands containing quinoline and pyridine terminal groups and their transition metal complexes. Inorg. Chem. Commun. 374 (2011) 269–277. (c) B. Baviskar, B. Baviskar, S. Chuadhary, K. Parwani, P. Balani, V. Salode, S. Patil, S. S. Khadabadi. Synthesis, characterization and anti-microbial screening of novel thiazolidino-fused compounds. J. Phar. Chem. 3(3) (2009) 91-95.

[18] R. A. Fromtling, J. N. Galgiani, M. A. Pfaller, A. Espinel-Ingroff, K. F. Bartizal, M. S. Bartlett, B. A. Body, C. Frey, G. Hall, G. D. Roberts, F. B. Nolte, E. C. Odds, M. G. Rinaldi, A. M. Suger, K. Villareal, Multicenter evaluation of a broth macrodilution antifungal susceptibility test for yeasts. Antimicrob Agents Chemother 37(1) (1993)39-45.

[19] G. M. Sheldrick. SHELXS–97, Program for solution of crystal structures. University of Göttingen, Germany (1997).

[20] G. M. Sheldrick. SHELXL–97, Program for refinement of crystal structures. University of Göttingen, Germany (1997).

[21] A. L. Spek. Single-crystal structure validation with the program PLATON. J. Apll. Crystallogr. 36(1) (2003) 7-13.

Table of Contents graphic and synopsis

Figure **1** Synthetic route of the ligand.

Figure **2** (a) View of the coordination environment of Mn (II) ions in **1** (H atoms are omitted for clarity). (b) View of the hydrogen-bonding between the mononuclear units in **1**. (c) View of the 2D hydrogen-bonding network of **1**.

Figure **3** (a) View of the coordination environment of Cd (II) ions in **2** (H atoms are omitted for clarity). (b) View of the hydrogen-bonding between the mononuclear units in **2**. (c) View of the 2D hydrogen-bonding network of **2**.

Figure **4** Large voids formed during the crystal packing in complexes **1** and **2.**

Table **1** Tests of MIC (μg/mL) of the ligand and complexes against bacterial and fungal strains [a]

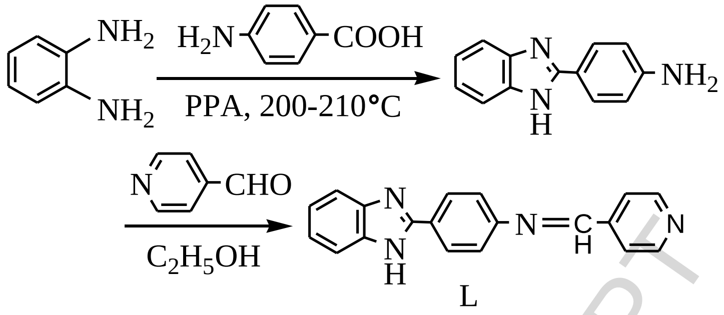
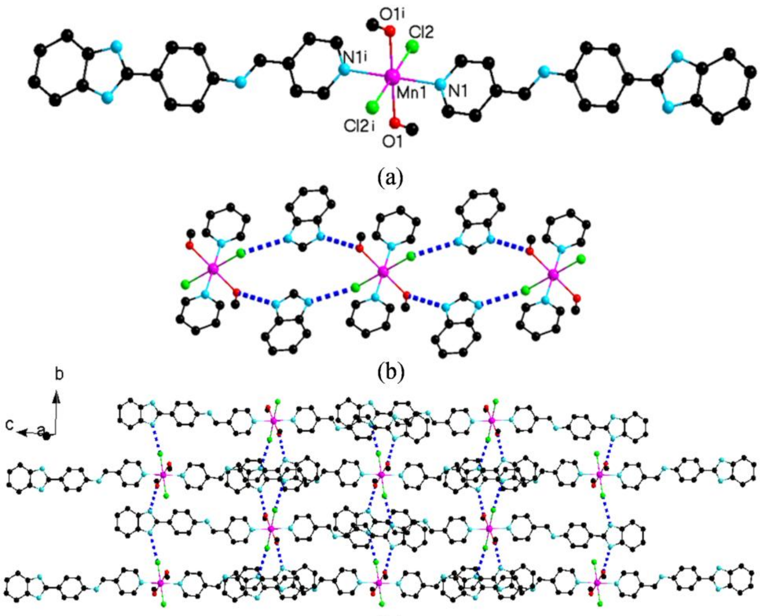


Figure **1**

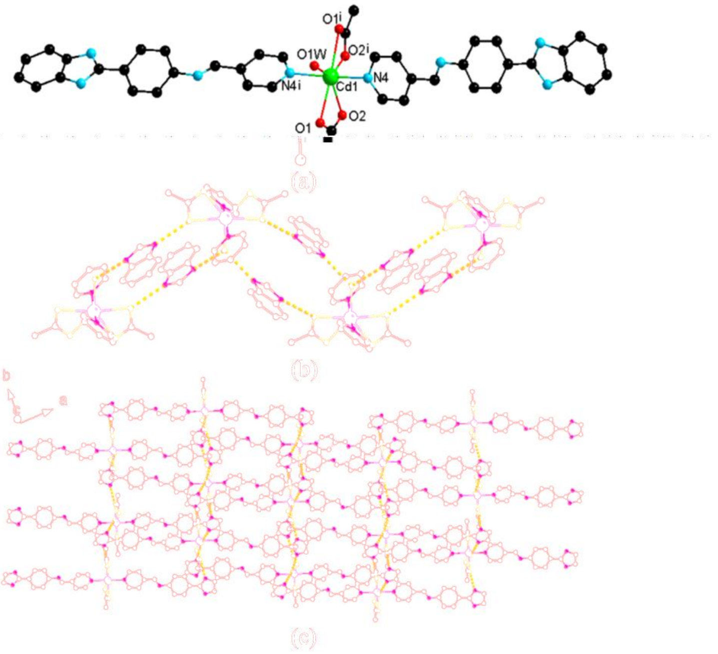


(a)

(b)

(c)

Figure **2**



(a)

(b)

(c)

Figure **3**

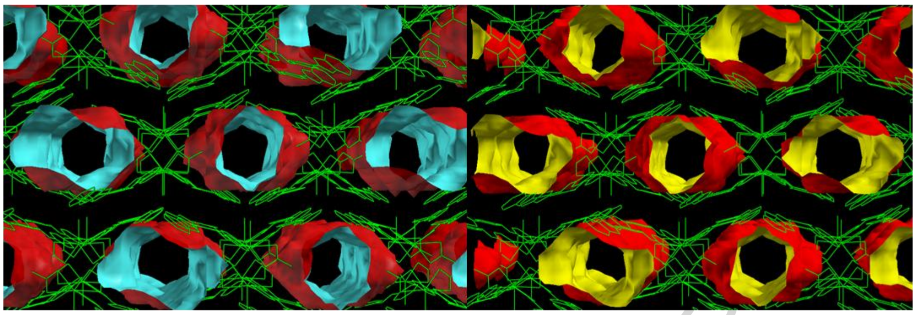


Figure **4**

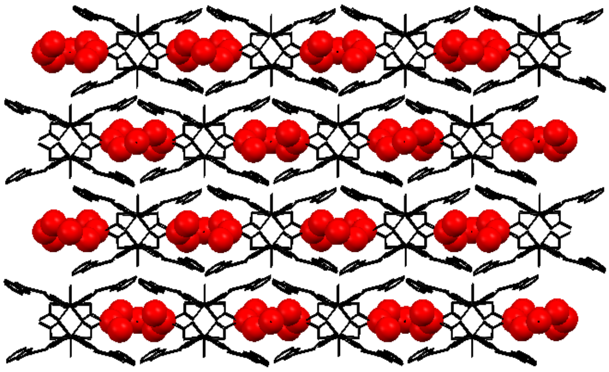


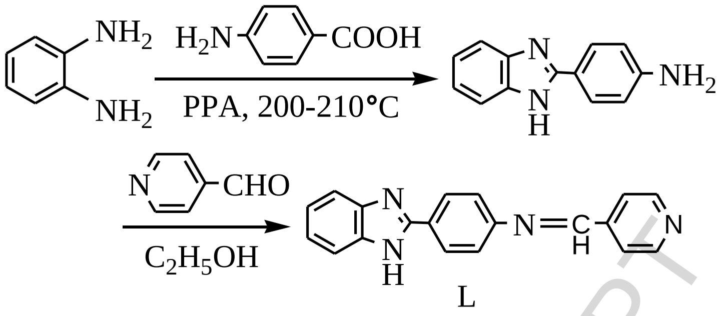
Figure **S1**

Table **1** Tests of MIC (μg/mL) of the ligand and complexes against bacterial and fungal strains [a]

Strains	Compounds					
	L	**1**	**2**	Amp [b]	Str [b]	Nys [b]
S. aureus ATCC 27154 (G^+)	25	12.5	6.25	3.1	12.5	NT
E. coli ATCC 25922 (G^-)	>50	3.13	>50	12.5	25	NT
P. aeruginosa (G^-)	>50	6.25	1.56	25	12.5	NT
S. ureae (G^+)	>50	12.5	12.5	50	6.25	NT
A. niger	>125	>125	>125	NT	NT	3.9
S. cerevisiae	>125	>125	>125	NT	NT	3.9
F. oxysporum f. sp. cubense	>125	>125	>125	NT	NT	7.8

[a] Results are expressed as the minimum inhibitory concentration (MIC).

[b] Ampicillin (Amp), Streptomycin sulfate (Str), Nystatin (Nys): positive control; NT, not tested.



Graphical abstract

Research Highlights

The research highlights in this manuscript are listed as following:

(1) The asymmetrical Schiff base ligand was synthesized.

(2) Two new complexes based on an asymmetrical Schiff base ligand were synthesized.

(3) The antibacterial and antifungal activities were determined.