

Synthesis, characterization and crystal structures of four copper(II) complexes derived from tridentate Schiff bases with urease inhibitory activity

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Abstract

Four Cu(II) complexes, $[\text{CuL}^1(\mu_{1,3}\text{-N}_3)]_n$ (**1**), $[\text{CuL}^1(\mu_{1,3}\text{-NCS})]_n$ (**2**), $[\text{Cu}_2(\mu\text{-Br})(\text{L}^2)_2(\mu_{1,1}\text{-N}_3)]$ (**3**), and $[\text{Cu}_2(\mu\text{-Cl})(\text{L}^2)_2(\mu_{1,1}\text{-N}_3)]$ (**4**), derived from the Schiff bases 2-bromo-6-(((2-(dimethylamino)ethyl)imino)methyl)phenol (HL^1) and 2-bromo-6-(((3-(methylamino)propyl)imino)methyl)phenol (HL^2), were synthesized and characterized by elemental analysis, IR and UV-Vis spectroscopy, as well as single crystal X-ray diffraction. Complexes **1** and **2** featured extended polynuclear Cu(II) architectures supported by $\mu_{1,3}$ -azide and $\mu_{1,3}$ -thiocyanate bridges, respectively, whereas **3** and **4** contained dinuclear Cu(II) units simultaneously bridged by end-on azide and halide ions. The urease inhibitory activities revealed a pronounced enhancement upon Cu(II) coordination. Complexes **1** and **2** exhibited excellent inhibition, with IC_{50} values of 0.2 ± 0.1 and $0.3 \pm 0.1 \mu\text{mol L}^{-1}$, respectively, whereas **3** and **4** showed moderate activities with IC_{50} values of 15 ± 2 and $14 \pm 2 \mu\text{mol L}^{-1}$. The results highlight the important role of the Schiff base framework and Cu(II) coordination environment in modulating urease inhibition.

Introduction

Schiff bases represent an important class of versatile ligands because their readily tunable donor sets, structural flexibility and diverse coordination modes enable the construction of metal complexes with rich structural architectures and attractive physicochemical properties [1–3]. In particular, Schiff bases containing phenolate and imine donors are highly effective in stabilizing Cu(II) centers and can readily form mononuclear, dinuclear and polynuclear coordination assemblies through the incorporation of additional bridging ligands [4–6]. The structural diversity of Cu(II) Schiff base complexes is not only of fundamental interest in coordination chemistry but also provides opportunities for developing functional materials and bioactive metal complexes.

Anion-assisted coordination assembly is an effective strategy for controlling the nuclearity and dimensionality of metal complexes. Auxiliary anions such as azide, thiocyanate and halide ions can participate directly in metal coordination and exhibit diverse bridging modes, including end-on and end-to-end azide bridges, N,S-bridging thiocyanate, and halide bridges [7, 8]. Small changes in the nature of these anions can therefore produce pronounced changes in metal–metal connectivity and overall molecular architecture. Among them, azide is particularly attractive because of its flexible coordination behavior, whereas thiocyanate can bridge metal centers through either its N or S terminus. Halide ions can also function as efficient bridges between Cu(II) centers and provide an additional structural parameter for tuning coordination geometry and nuclearity. Nevertheless, the controlled assembly of Cu(II) Schiff base complexes through different combinations of these auxiliary anions remains insufficiently explored, particularly when structural changes are considered together with biological properties.

In parallel with their structural diversity, transition metal Schiff base complexes have attracted considerable attention as potential enzyme inhibitors. Urease (EC 3.5.1.5), a nickel-dependent metalloenzyme that catalyzes the hydrolysis of urea to ammonia and carbon dioxide, plays important roles in the pathogenicity of several microorganisms and in nitrogen metabolism [9, 10]. Excessive urease activity can lead to undesirable physiological and environmental consequences, making urease an important target for the development of inhibitors. Acetohydroxamic acid is a well-known urease inhibitor; however, its limitations have stimulated the search for alternative compounds with higher inhibitory efficiency and improved structural diversity. Coordination of organic ligands to transition metal ions provides an attractive approach because metal incorporation can substantially modify ligand geometry and interaction with the enzyme active site. Accordingly, Cu(II) complexes containing Schiff base ligands have emerged as promising candidates for the development of new urease inhibitors [11–13].

Despite these advances, the relationship between the coordination assembly directed by auxiliary anions and the resulting urease inhibition has received comparatively less attention. In particular, it remains interesting to determine whether changing the bridging mode from μ -1,3 azide to μ -1,3 thiocyanate, or introducing simultaneous halide and azide bridges, can generate structurally distinct Cu(II) assemblies while retaining or enhancing biological activity. Such a comparison is valuable because it allows the influence of coordination nuclearity and bridging topology on the biological behavior of closely related Cu(II) complexes to be evaluated within a single study.

In this work, we therefore designed and synthesized four Cu(II) complexes $[\text{CuL}^1(\mu_{1,3}\text{-N}_3)]_n$ (**1**), $[\text{CuL}^1(\mu_{1,3}\text{-NCS})]_n$ (**2**), $[\text{Cu}_2(\mu\text{-Br})(\text{L}^2)_2(\mu_{1,1}\text{-N}_3)]$ (**3**), and $[\text{Cu}_2(\mu\text{-Cl})(\text{L}^2)_2(\mu_{1,1}\text{-N}_3)]$ (**4**), based on Schiff bases 2-bromo-6-(((2-(dimethylamino)ethyl)imino)methyl)phenol (HL^1) and 2-bromo-6-(((3-(methylamino)propyl)imino)methyl)phenol (HL^2) and different auxiliary anions. Complexes **1** and **2** were obtained from HL^1 with CuBr_2 in the presence of azide and thiocyanate, respectively, whereas complexes **3** and **4** were constructed from HL^2 and NaN_3 with CuBr_2 and CuCl_2 , respectively. Single crystal X-ray diffraction revealed that complexes **1** and **2** are extended polynuclear Cu(II) assemblies through end-to-end azide and thiocyanate bridges, respectively, while complexes **3** and **4** exhibited dinuclear Cu(II) units supported by the simultaneous end-on azide and μ_2 -halide bridges. The structures were further characterized by infrared and UV–visible spectroscopy. Importantly, the urease inhibitory activities of all four complexes were evaluated.

Experimental

Materials and measurements

All reagents and solvents were of analytical grade and used as received without further purification. 3-Bromosalicylaldehyde, *N,N*-dimethylethane-1,2-diamine, and *N*-methylpropane-1,3-diamine were purchased from Macklin Chemical Co., Ltd. Copper(II) bromide, copper(II) chloride, sodium azide, and

ammonium thiocyanate were supplied by Liaodong Chemical Co. Ltd. Urea was obtained from Sigma Aldrich (St. Louis, USA). All other chemicals and solvents were commercially available and used without further purification. The Schiff bases were synthesized according to a previously reported procedure [14].

Elemental analyses for carbon, hydrogen, and nitrogen were performed using a Perkin–Elmer 240C elemental analyzer. FT-IR spectra were recorded on a Nicolet AVATAR 360 spectrophotometer using KBr pellets over the range of 4000–400 cm^{-1} . Electronic absorption spectra were measured with a Lambda 35 UV–Vis spectrophotometer. Molar conductivity measurements were carried out using a DDS-11A conductivity meter. Single crystal X-ray diffraction data were collected on a Bruker APEX II CCD diffractometer.

Synthesis of complexes 1 and 2

The Schiff base HL¹ (27 mg, 0.10 mmol) was dissolved in methanol, followed by the addition of CuBr₂ (22 mg, 0.10 mmol) and NaN₃ (6.5 mg, 0.10 mmol) or NH₄SCN (7.6 mg, 0.10 mmol). The resulting mixtures were stirred at room temperature for 1 h to facilitate the coordination and self-assembly processes. After filtration, the clear filtrates were allowed to stand undisturbed at room temperature for slow evaporation. Green single crystals of the complexes **1** and **2** suitable for X-ray diffraction analysis were obtained after several days. The crystals were collected by filtration, washed with a small amount of methanol, and dried in air.

Complex **1**: Yield: 28 mg (74%). Anal. Calcd for C₁₁H₁₄BrCuN₅O (%): C, 35.16; H, 3.76; N 18.64. Found (%): C, 34.93; H, 3.82; N, 18.55%. IR (KBr, cm^{-1}): 2044 (s), 1629 (vs), 1591 (m), 1404 (m), 685 (m), 461 (w). UV–Vis (λ_{max} , nm): 208, 270, 371. Complex **2**: Yield: 31 mg (79%). Anal. Calcd for C₁₂H₁₄BrCuN₃OS (%): C, 36.79; H, 3.60; N, 10.73. Found (%): C, 36.67; H, 3.53; N, 10.86. IR (KBr, cm^{-1}): 2093 (vs), 1636 (vs), 1591 (m), 1449 (m), 1319 (m), 1225 (m), 1130 (m), 742 (m), 461 (w). UV–Vis (λ_{max} , nm): 205, 269, 376.

Synthesis of complexes 3 and 4

The Schiff base HL² (27 mg, 0.10 mmol) was dissolved in methanol, followed by the addition of CuBr₂ (22 mg, 0.10 mmol) and NaN₃ (6.5 mg, 0.10 mmol) to afford complex **3**. For the synthesis of complex **4**, CuCl₂·2H₂O (17 mg, 0.10 mmol) and NaN₃ (0.10 mmol) were used under identical reaction conditions. The resulting mixtures were stirred at room temperature and then filtered. The clear filtrates were left undisturbed at room temperature to allow slow evaporation. Suitable single crystals were collected by filtration, washed with a small amount of methanol, and dried in air.

Complex **3**: Yield: 19 mg (48%). Anal. Calcd for C₂₂H₂₈Br₃Cu₂N₇O₂ (%): C, 33.48; H, 3.58; N, 12.42. Found (%): C, 33.57; H, 3.64; N, 12.28. IR (KBr, cm^{-1}): 3213 (w), 2077 (s), 1622 (vs), 1589 (s), 1523 (m), 1227 (s),

1132 (s), 1072 (m), 744 (s), 491 (w). UV–Vis (λ_{max} , nm): 205, 269, 373. Complex **4**: Yield: 21 mg (57%). Anal. Calcd for $\text{C}_{22}\text{H}_{28}\text{Br}_2\text{ClCu}_2\text{N}_7\text{O}_2$ (%): C, 35.47; H, 3.79; N, 13.16. Found (%): C, 35.60; H, 3.86; N, 13.03. IR (KBr, cm^{-1}): 3232 (w), 2072 (s), 1623 (vs), 1589 (m), 1520 (m), 1225 (s), 1129 (s), 1065 (m), 736 (s), 453 (w). UV–Vis (λ_{max} , nm): 212, 265, 372.

Crystal structure determination

Single crystals of the complexes suitable for X-ray diffraction analysis were selected and mounted on glass fibers for data collecting using a Bruker APEX II CCD area-detector diffractometer equipped with a fine-focus sealed tube and graphite-monochromated Mo K α radiation ($\lambda = 0.71073 \text{ \AA}$). Diffraction data were collected at 298(2) K and corrected for Lorentz and polarization effects, linear decay, and absorption effects using a multi-scan correction based on ω -scan data. The data were processed using the SMART and SAINT programs [15]. The crystal structures were solved by direct methods and refined by full-matrix least-squares refinement on F^2 using SHELXL, followed by successive difference Fourier syntheses [16]. All non-hydrogen atoms were refined with anisotropic displacement parameters. The amino hydrogen atoms of **3** and **4** were located from difference Fourier maps and refined isotropically, with the N–H distances restrained to 0.90(1) $\text{\AA}$. The remaining hydrogen atoms were generated geometrically and refined using the riding model. Selected crystallographic data and refinement parameters are listed in Table 1.

Table 1
Crystallographic and experimental data for the complexes

Formula	1	2	3	4
	C₁₁H₁₄BrCuN₅O	C₁₂H₁₄BrCuN₃OS	C₂₂H₂₈Br₃Cu₂N₇O₂	C₂₂H₂₈Br₂ClCu₂N₇O₂
Formula Weight	375.72	391.77	789.32	744.86
Crystal shape/color	Block/green	Block/green	Block/green	Block/green
Crystal size/mm ³	0.31·0.28·0.27	0.17·0.15·0.15	0.18·0.17·0.15	0.19·0.17·0.17
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>
<i>a</i> /Å	10.5370(11)	7.3120(12)	20.7992(16)	20.535(2)
<i>b</i> /Å	10.0646(11)	22.447(2)	12.9766(13)	12.8818(14)
<i>c</i> /Å	13.4315(12)	10.1240(13)	10.5297(11)	10.4591(13)
<i>α</i> /°	90	90	90	90
<i>β</i> /°	103.285(1)	96.950(2)	103.154(2)	102.369(2)
<i>γ</i> /°	90	90	90	90
<i>V</i> /Å ³	1386.3(2)	1649.4(4)	2767.4(5)	2702.4(5)
<i>Z</i>	4	4	4	4
<i>D_c</i> /(g/cm ⁻³)	1.800	1.578	1.894	1.831
<i>μ</i> /mm ⁻¹	4.457	3.868	5.902	4.664
<i>F</i> (000)	748	780	1552	1480
<i>θ</i> range/°	2.55–25.50	1.81–25.50	1.00–25.50	1.02–25.50
Reflections	8036	9205	14487	13898
Unique reflections	2582	3062	5159	5024
Observed reflections (<i>I</i> ≥ 2σ(<i>I</i>))	2060	2324	3915	2878
Parameters	174	174	333	333

Formula	1	2	3	4
	$\text{C}_{11}\text{H}_{14}\text{BrCuN}_5\text{O}$	$\text{C}_{12}\text{H}_{14}\text{BrCuN}_3\text{OS}$	$\text{C}_{22}\text{H}_{28}\text{Br}_3\text{Cu}_2\text{N}_7\text{O}_2$	$\text{C}_{22}\text{H}_{28}\text{Br}_2\text{ClCu}_2\text{N}_7\text{O}_2$
Restraints	0	0	2	2
Goodness-of-fit on F^2	1.027	1.080	1.017	1.034
R_1, wR_2 [$I \geq 2\sigma(I)$]	0.0362, 0.0858	0.0695, 0.2071	0.0324, 0.0664	0.0832, 0.1967
R_1, wR_2 (all data)	0.0493, 0.0929	0.0907, 0.2229	0.0522, 0.0757	0.1464, 0.2349

Urease inhibitory activity assay

The urease inhibitory activity was evaluated according to the literature method [17]. Briefly, 75 μL of *Jack bean* urease solution and 75 μL of the tested compound at different concentrations in DMSO were mixed in a 96-well microplate and preincubated for 15 min at room temperature. Acetohydroxamic acid was used as the reference inhibitor. Subsequently, 75 μL of phosphate buffer (pH 6.8) containing phenol red (0.18 mmol L^{-1}) and urea (400 mmol L^{-1}) was added to each well. The reaction was monitored at 560 nm using a microplate reader, and the time required for the urease-catalyzed hydrolysis of urea to increase the pH from 6.8 to 7.7 was recorded. The endpoint was determined from the color change of phenol red indicator.

Results and discussion

Chemistry

Complexes **1–4** were readily synthesized under mild solution conditions by reacting the corresponding Schiff base with Cu(II) salts and auxiliary anions in methanol at room temperature, followed by slow evaporation of the resulting solutions. Complexes **1** and **2** were obtained from HL¹ and CuBr₂ in the presence of NaN₃ and NH₄SCN, respectively, whereas complexes **3** and **4** were prepared from HL² using CuBr₂/NaN₃ and CuCl₂/NaN₃, respectively. All reactions were carried out with a 1:1:1 molar ratio of Schiff base, Cu(II) salt and auxiliary anion.

The nature of the Cu(II) precursor and auxiliary anion exerted a pronounced influence on the coordination self-assembly and the resulting nuclearity. In **1**, the azide anion adopted an end-to-end μ -1,3 bridging mode, giving rise to an extended polynuclear Cu(II) architecture. Replacement of azide by thiocyanate afforded **2**, in which the thiocyanate anion also acted as a μ -1,3 bridge through its N and S donor atoms, generating a related polynuclear Cu(II) assembly. In contrast, the azide anion in **3** and **4** adopted an end-on μ -1,1 bridging mode, while the bromide and chloride ions additionally acted as μ ₂-Br

and μ_2 -Cl bridges, respectively. This combination of bridging modes resulted in discrete dinuclear Cu(II) units in both complexes. These structural variations demonstrate that subtle changes in the metal precursor and auxiliary anion can effectively modulate the bridging modes and nuclearity of the resulting Cu(II) assemblies.

The molar conductivity of complexes **1–4** was measured in a 1×10^{-3} mol L⁻¹ solution of DMSO/H₂O solution (V:V = 1:99). The conductivity values of 23–37 Ω^{-1} cm² mol⁻¹ indicated that all four complexes behave as non-electrolytes in solution [23].

Structure description of complexes **1** and **2**

The molecular structures of complexes **1** and **2** are shown in Figs. 1 and 2, respectively, and selected bond lengths and angles are listed in Table 2. Single crystal X-ray diffraction analysis revealed that both complexes exhibited extended Cu(II) coordination assemblies in which the deprotonated Schiff base ligand and auxiliary anions cooperatively supported the Cu(II) centers. In both complexes, each Cu(II) ion is coordinated by one deprotonated Schiff base ligand through the phenolate O atom, imine N atom, and amine N atom, thus adopting an N,N,O-tridentate coordination mode. The Cu–O and Cu–N bond lengths are within the ranges commonly observed for Cu(II) complexes [18, 19]. For **1**, the Cu1–O1, Cu1–N1, and Cu1–N2 bond lengths are 1.900(3), 1.958(3), and 2.054(3) Å, respectively, whereas the corresponding distances in **2** are 1.912(5), 1.938(6), and 2.070(7) Å.

Table 2
Selected bond lengths/Å and angles/° for complexes **1** and **2**

Cu1–O1	1	2
	1.900(3)	1.913(5)
Cu1–N1	1.957(3)	1.938(6)
Cu1–N2	2.053(3)	2.070(7)
Cu1–N3	1.965(3)	1.972(7)
Cu1–N5A/S1A	2.449(3)	2.844(7)
O1–Cu1–N1	92.44(12)	92.6(2)
O1–Cu1–N3	91.36(13)	91.1(2)
N1–Cu1–N3	166.65(15)	168.4(3)
O1–Cu1–N2	174.47(12)	172.2(3)
N1–Cu1–N2	84.36(12)	83.8(3)
N3–Cu1–N2	90.78(13)	91.1(3)
O1–Cu1–N5A/S1A	94.27(12)	92.6(3)
N1–Cu1–N5A/S1A	90.74(13)	91.0(3)
N3–Cu1–N5A/S1A	101.74(15)	99.7(3)
N2–Cu1–N5A/S1A	90.29(12)	94.4(3)
Symmetry codes for A: N5A for 1 : $1 - x, -1/2 + y, 1/2 - z$; S1A for 2 : $1/2 + x, 1/2 - y, 1/2 + z$.		

Table 3
Selected bond lengths/Å and angles/° for
complexes **3** and **4**

Cu1–O1	3	4
	1.924(2)	1.923(7)
Cu1–N1	1.962(3)	1.960(10)
Cu1–N2	2.036(3)	2.034(9)
Cu1–N5	2.042(3)	2.054(10)
Cu1–Br3/Cl3	2.7537(6)	2.584(3)
Cu2–O2	1.925(2)	1.929(7)
Cu2–N3	1.960(3)	1.957(10)
Cu2–Br3/Cl3	2.8123(7)	2.666(3)
Cu2–N5	2.032(3)	2.025(10)
Cu2–N4	2.034(3)	2.049(9)
O1–Cu1–N1	92.83(12)	92.6(4)
O1–Cu1–N2	165.99(12)	167.1(4)
N1–Cu1–N2	96.02(13)	96.2(4)
O1–Cu1–N5	84.92(11)	85.3(3)
N1–Cu1–N5	170.73(13)	169.1(4)
N2–Cu1–N5	84.61(12)	84.4(4)
O1–Cu1–Br3/Cl3	100.46(8)	99.9(2)
N1–Cu1–Br3/Cl3	98.24(9)	100.0(3)
N2–Cu1–Br3/Cl3	89.02(9)	87.9(3)
N5–Cu1–Br3/Cl3	91.01(9)	91.0(3)
O2–Cu2–N3	92.46(12)	92.5(4)
O2–Cu2–N5	85.38(11)	85.1(3)
N3–Cu2–N5	175.20(13)	175.7(4)
O2–Cu2–N4	166.55(14)	166.2(4)
N3–Cu2–N4	94.29(14)	94.6(4)
Br3 for 3 , Cl3 for 4 .		

Cu1–O1	3	4
	1.924(2)	1.923(7)
N5–Cu2–N4	86.99(13)	87.1(4)
O2–Cu2–Br3/Cl3	99.96(9)	100.8(3)
N3–Cu2–Br3/Cl3	95.04(10)	94.6(3)
N5–Cu2–Br3/Cl3	89.56(9)	89.3(3)
N4–Cu2–Br3/Cl3	91.02(10)	90.4(3)
Br3 for 3 , Cl3 for 4 .		

The remaining two coordination sites around Cu(II) are occupied by donor atoms from the bridging auxiliary anions. In **1**, one terminal N atom of an azide anion (N3) coordinates to Cu1 with a Cu1–N3 distance of 1.963(3) Å, while the terminal N atom (N5) of a symmetry-related azide anion is weakly coordinated to Cu1 at 2.450(3) Å. In **2**, one terminal N atom of a thiocyanate anion (N3) is directly coordinated to Cu1 with a Cu1–N3 distance of 1.972(7) Å, whereas the S atom (S1) of a symmetry-related thiocyanate anion interacted with Cu1 at a considerably longer distance of 2.843(4) Å. Accordingly, the azide and thiocyanate anions act as μ -1,3 bridges in **1** and **2**, respectively. The azide ligand connected adjacent Cu(II) centers through its two terminal N atoms, whereas the thiocyanate ligand links neighboring Cu(II) ions through its N and S donor atoms. These bridging interactions extend the individual Cu-Schiff base units into polynuclear coordination architecture.

Each Cu(II) center is consequently five-coordinate and adopted a distorted square-pyramidal geometry. The four relatively strongly coordinated donor atoms, O1, N1, N2 and N3, approximately define the basal plane, while the symmetry-related N5 atom of the azide ligand in **1** or S1 atom of the thiocyanate ligand in **2** occupy the apical position. The basal plane geometry is supported by the nearly linear *trans* angles O1–Cu1–N2 = 174.47(14)° and N1–Cu1–N3 = 166.61(13)° for **1**, and O1–Cu1–N2 = 172.23(18)° and N1–Cu1–N3 = 168.43(18)° for **2**. The significantly longer apical Cu1–N5 distance in **1** and Cu1–S1 distance in **2**, compared with the corresponding basal Cu–N/O bonds, indicated pronounced axial elongation. This feature is consistent with the characteristic coordination preferences of Cu(II), and contributes to the observed distortion from an ideal square-pyramidal geometry.

Structure description of complexes **3** and **4**

The molecular structures of complexes **3** and **4** are shown in Figs. 3 and 4, respectively, with selected bond lengths and angles listed in Table 2. In contrast to the extended coordination architectures observed for **1** and **2**, complexes **3** and **4** adopt discrete dinuclear Cu(II) structures in which the two metal centers are simultaneously supported by halide and azide bridges. The halide bridges are bromide in **3** and chloride in **4**. In both complexes, the asymmetric unit contains two crystallographically independent Cu(II) centers (Cu1 and Cu2) and two Schiff base ligands. Each Schiff base ligand

coordinates to a single Cu(II) center through the phenolate O, imine N, and amine N atoms, giving an N,N,O-tridentate chelating mode.

The two Cu(II) centers are additionally linked by one halide and one azide anion. In **3**, Br₃ functions as a μ_2 -Br bridge, with Cu1–Br3 and Cu2–Br3 distances of 2.7537(6) and 2.8122(7) Å, respectively, whereas the corresponding μ_2 -Cl bridge in **4** exhibits Cu1–Cl3 and Cu2–Cl3 distances of 2.584(3) and 2.666(3) Å, respectively. The azide anion adopts a μ_2 -1,1 (end-on) bridging mode, with both Cu centers bonded to the same terminal nitrogen atom (N5). The Cu–N5 distances are 2.042(3) and 2.032(3) Å for Cu1 and Cu2, respectively, in **3**, and 2.054(10) and 2.025(10) Å, respectively, in **4**.

Accordingly, each Cu(II) center is five-coordinate and is surrounded by the three donor atoms of the Schiff base ligand, and one auxiliary donor atom. The coordination environment can be described as distorted square pyramid. In the basal plane of **3**, the *trans* angles around Cu1 are 170.73(12)° and 165.96(10)°, while those around Cu2 are 175.20(12)° and 166.60(10)°. The corresponding *trans* angles in **4** are 169.10(37)° and 167.17(30)° for Cu1 and 175.70(42)° and 166.15(31)° for Cu2. The remaining *cis* angles are close to 90°, further supporting the distorted square pyramidal assignment.

Thus, the dinuclear cores of **3** and **4** can be described as Cu₂(μ -Br)($\mu_{1,1}$ -N₃) and Cu₂(μ -Cl)($\mu_{1,1}$ -N₃) units, respectively, with each Cu(II) center further stabilized by an N,N,O-tridentate Schiff base ligand. The coexistence of μ -halide and $\mu_{1,1}$ -azide bridges is a notable structural feature of these complexes and results in discrete dinuclear architectures, in contrast to the azide-bridged extended coordination structures observed for **1** and **2**.

IR and UV-Vis spectra

The IR spectra of complexes **1–4** display the characteristic bands of the tridentate Schiff base ligands together with those associated with the azide or thiocyanate auxiliary ligands. The azomethine $\nu(\text{C}=\text{N})$ stretching vibration is observed at 1629, 1636, 1622 and 1623 cm^{−1} for **1–4**, respectively [20]. The aromatic C = C vibrations occur at 1589–1591 cm^{−1}, while the phenolate $\nu(\text{C}-\text{O})$ and $\nu(\text{C}-\text{N})$ vibrations appear in the ranges 1225–1319 and 1126–1132 cm^{−1}, respectively. Complexes **3** and **4** exhibit $\nu(\text{N}-\text{H})$ bands at 3213 and 3232 cm^{−1}, respectively, whereas no corresponding absorption is detected for **1** and **2**, in agreement with the different diamine substituents of the Schiff base ligands. The absence of $\nu(\text{O}-\text{H})$ bands in all four complexes further supports deprotonation of the phenolic groups and coordination of the Schiff bases in their phenolate forms. Weak bands observed at 461–491 cm^{−1} are tentatively assigned to Cu–N and/or Cu–O vibrations.

The characteristic stretching vibrations of the auxiliary pseudo-halide ligands provide useful information on their coordination modes. For **2**, a strong absorption at 2093 cm^{−1} is assigned to $\nu(\text{C}\equiv\text{N})$ of the coordinated thiocyanate ligand, while the band at 742 cm^{−1} is attributed to $\nu(\text{C}-\text{S})$ [21]. The azide-containing complexes **1**, **3** and **4** show $\nu_{\text{as}}(\text{N}_3)$ bands at 2044, 2077 and 2072 cm^{−1}, respectively [22]. The relatively higher frequencies observed for **3** and **4** are consistent with the end-on (μ -1,1) bridging

mode of the azide ligand, whereas the lower-frequency band in **1** is consistent with its end-to-end (μ -1,3) bridging mode. These assignments are in good agreement with the coordination modes established by single crystal X-ray diffraction.

The electronic absorption spectra of **1–4** exhibit broadly similar features owing to their common salicylaldehyde chromophore. The intense absorption bands at 208, 205, 203 and 212 nm for **1–4**, respectively, are assigned to ligand-centered $\pi \rightarrow \pi^*$ transitions involving the aromatic and azomethine chromophores. The shoulders observed at 270 nm for **1–3** and 265 nm for **4** can likewise be attributed to $\pi \rightarrow \pi^*$ transitions associated with the azomethine moiety. The broad absorption centered at 371, 376, 373 and 372 nm for **1–4**, respectively, are tentatively assigned to ligand-to-metal charge transfer (LMCT) transitions, most plausibly involving electron transfer from the phenolate oxygen donor atoms to the Cu(II) centers. The close similarity of these spectral features is consistent with the related Cu(II) coordination environments and common Schiff base chromophore in the four complexes.

Urease inhibitory activity

The urease inhibitory activities of HL¹, HL², complexes **1–4**, CuBr₂, and acetohydroxamic acid are summarized in Table 4. At 100 $\mu\text{mol L}^{-1}$, the free Schiff bases HL¹ and HL² showed weak inhibition ($15 \pm 1\%$ and $21 \pm 1\%$, respectively), whereas Cu(II) coordination markedly enhanced the activity. Complexes **1** and **2** were particularly potent, with inhibition rates of $98 \pm 2\%$ and $97 \pm 2\%$ and IC₅₀ values of 0.2 ± 0.1 and $0.3 \pm 0.1 \mu\text{mol L}^{-1}$, respectively. Complexes **3** and **4** were less active, giving IC₅₀ values of 15 ± 2 and $14 \pm 2 \mu\text{mol L}^{-1}$, respectively, but remained more effective than acetohydroxamic acid (IC₅₀ = $23 \pm 1 \mu\text{mol L}^{-1}$). For comparison, CuBr₂ showed an IC₅₀ of $5 \pm 1 \mu\text{mol L}^{-1}$. These results clearly demonstrate that coordination to Cu(II), particularly in complexes **1** and **2**, substantially improves the urease inhibitory ability of the Schiff base ligands.

Table 4
Urease inhibition of the compounds

Tested materials	Percentage Inhibition ^a	IC ₅₀ (μmol L ⁻¹)
HL ¹	15 ± 1	–
HL ²	21 ± 1	–
1	98 ± 2	0.2 ± 0.1
2	97 ± 2	0.3 ± 0.1
3	72 ± 3	15 ± 2
4	75 ± 3	14 ± 2
CuBr ₂	91 ± 2	5 ± 1
Acetohydroxamic acid	85 ± 3	23 ± 1
^a The concentration is 100 μmol L ⁻¹ . – means no activity or IC ₅₀ > 100 μmol L ⁻¹ .		

The enhanced activity of the Cu(II) complexes is consistent with previous reports, in which Schiff base Cu(II) complexes generally exhibited stronger urease inhibition than their corresponding free ligands, with reported IC₅₀ values ranging from the submicromolar to low-micromolar level [23, 24]. The activity of complex **1** (IC₅₀ = 0.20 μmol L⁻¹) is comparable to that of the highly active aroylhydrazone Cu(II) complex [CuClL]·CH₃OH (IC₅₀ = 0.20 μmol L⁻¹) [25], and comparable to some high effective Cu(II) complexes with Schiff base ligands [26, 27]. Thus, complexes **1** and **2** can be considered highly potent Cu(II)-based urease inhibitors.

Comparison of complexes **1** and **2** indicates that the azido and thiocyanato bridging ligands have little influence on urease inhibition, as their activities are essentially comparable. Similarly, complexes **3** and **4** exhibit only a minor difference in activity upon replacing the bromide bridge with chloride. In contrast, the much higher activities of **1** and **2** relative to **3** and **4** suggest that the nature of the Schiff base ligand and the resulting Cu(II) coordination environment play a more important role than the identity of the bridging anion. The activity of CuBr₂ further indicates that the Cu(II) center itself contributes to urease inhibition, while an appropriate ligand environment can greatly enhance this intrinsic activity. Overall, these results highlight aminoalkyl-substituted Schiff base Cu(II) complexes, particularly **1** and **2**, as promising urease inhibitors.

Conclusion

In conclusion, four Cu(II) complexes featuring diverse coordination motifs were synthesized and characterized. Their structures were influenced by both the nature of the Schiff base ligand and the

auxiliary anion. Urease inhibition assays revealed a pronounced improvement in activity upon metal coordination. Complexes **1** and **2** were especially effective, exhibiting submicromolar IC_{50} values and significantly higher than $CuBr_2$ and acetohydroxamic acid, whereas complexes **3** and **4** showed moderate inhibitory potency. The close activities observed for **1** versus **2** and **3** versus **4** suggest that changing the bridging anion has only a limited effect on urease inhibition. In contrast, the Schiff base framework and the associated Cu(II) coordination environment appear to be more decisive in determining the inhibitory performance. These results demonstrate that aminoalkyl-substituted Schiff base Cu(II) complexes, particularly the L^1 -derived systems, represent promising candidates for further development as urease inhibitors.

Declarations

Competing interests

The authors declare no competing interests.

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Author Contribution

Yang-Lei Li: Writing the main manuscript, synthesis and characterization. Zi-Han Pu and Fei-Yang Xie: Chemical synthesis and characterization. Zhong-Lu You: Conception, supervision, writing, validation, methodology, investigation, biological assay.

Data availability

No datasets were generated or analysed during the current study.

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Schemes

Schemes 1 and 2 are available in the Supplementary Files section

Figures

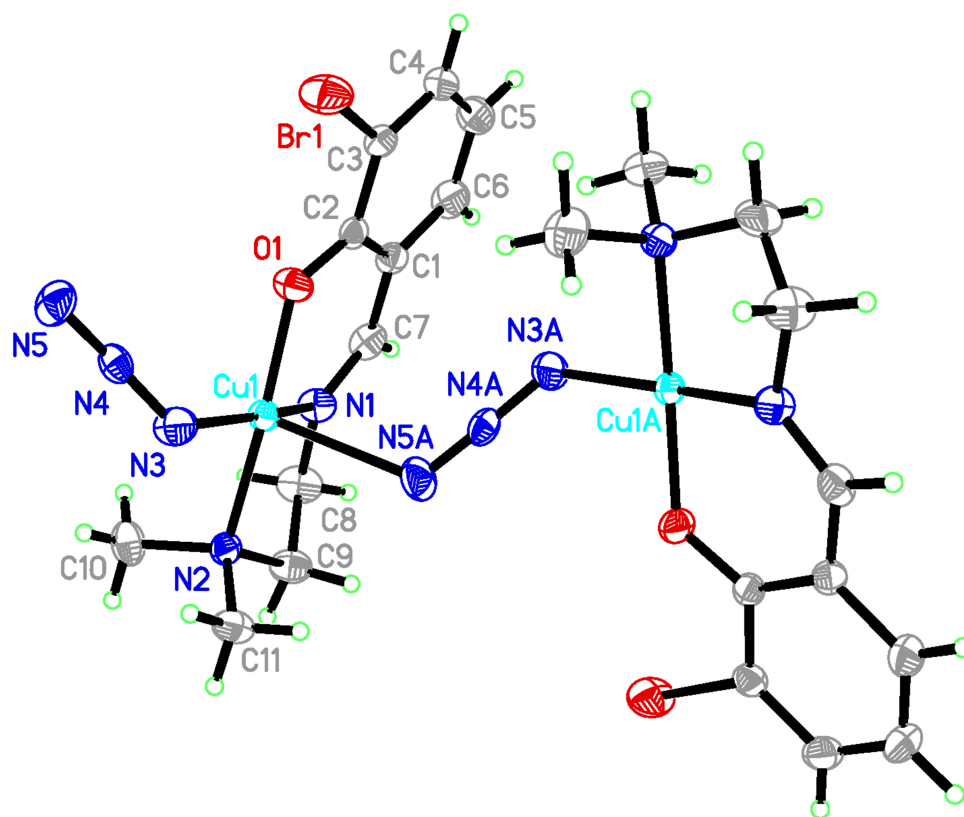


Figure 1

Molecular structure of complex **1**. Displacement ellipsoids for non-hydrogen atoms are drawn at the 30% probability level. Symmetry code: A: $1 - x, -1/2 + y, 1/2 - z$.

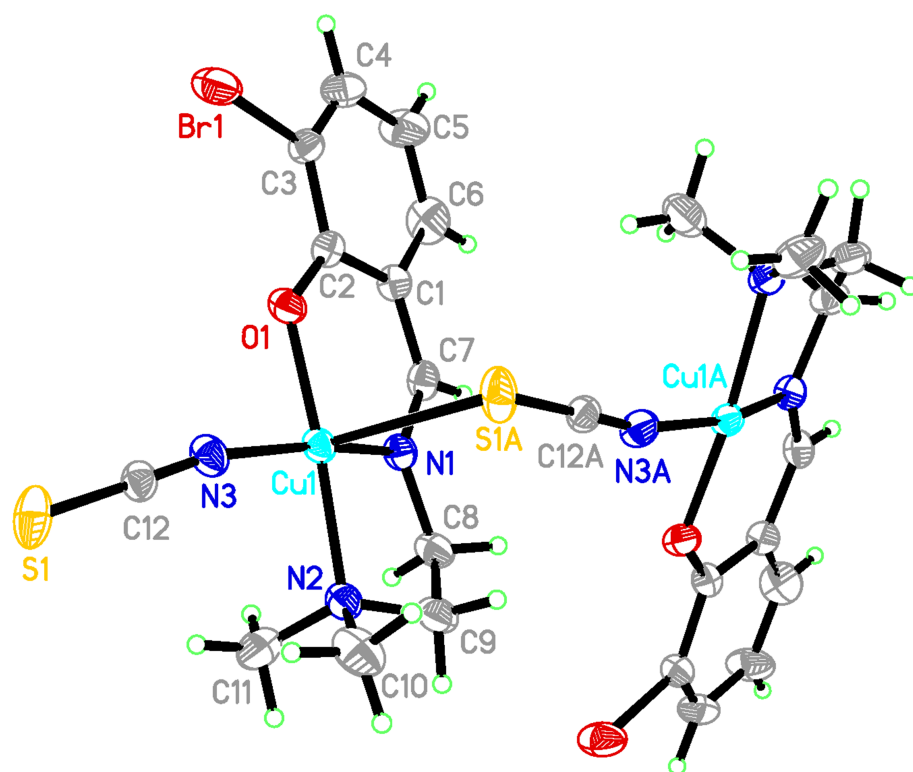


Figure 2

Molecular structure of complex **2**. Displacement ellipsoids for non-hydrogen atoms are drawn at the 30% probability level. Symmetry code: A: $1/2 + x$, $1/2 - y$, $1/2 + z$.

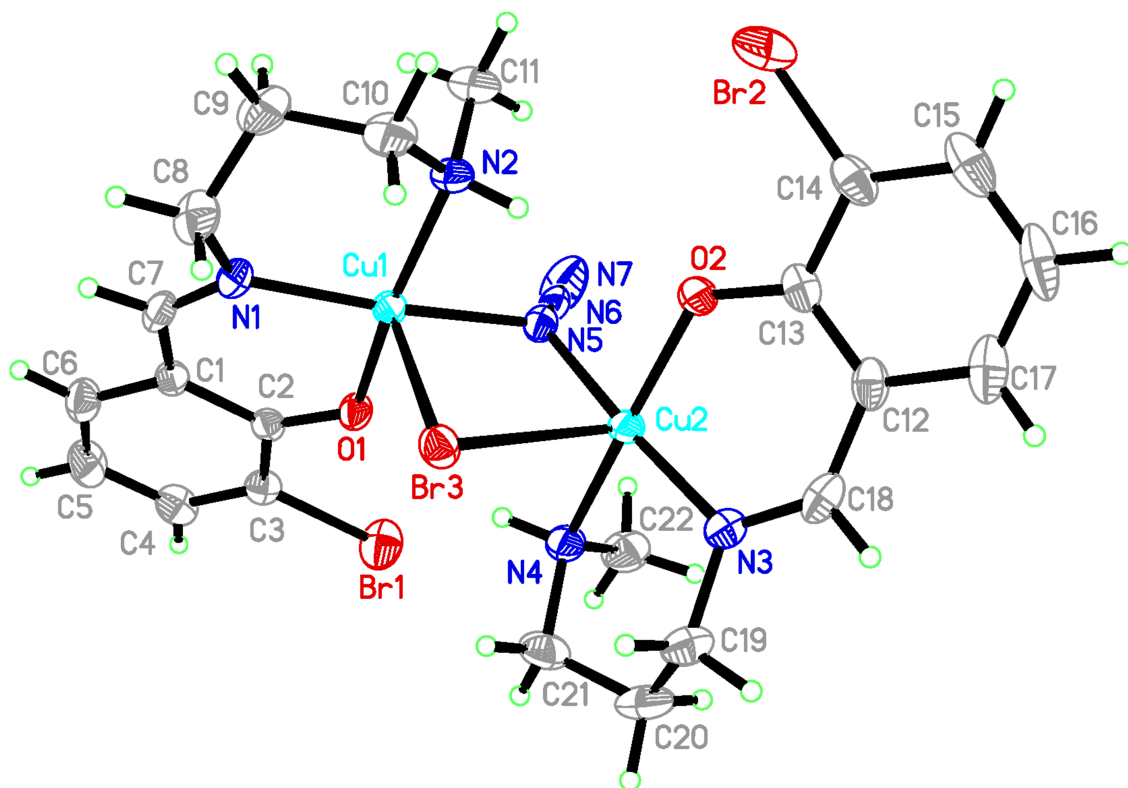


Figure 3

Molecular structure of complex **3**. Displacement ellipsoids for non-hydrogen atoms are drawn at the 30% probability level.

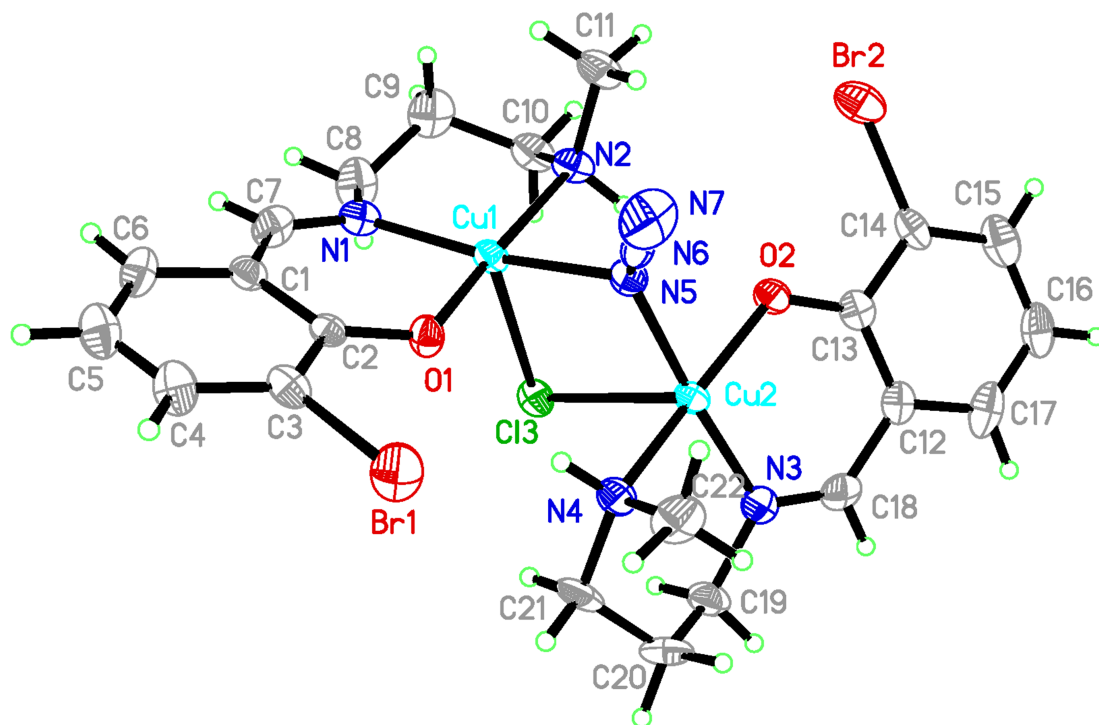


Figure 4

Molecular structure of complex **4**. Displacement ellipsoids for non-hydrogen atoms are drawn at the 30% probability level.

Supplementary Files

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