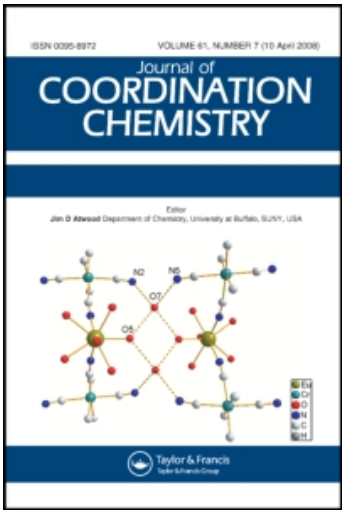

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

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To cite this Article Tong-Tao, Xu , Jian, Gao , Xing-You, Xu , Xu-Jie, Yang , Lu-De, Lu and Wang, Xin(2007) 'Synthesis, structure and antimicrobial study of two copper(II) complexes derived from paeonol and *R*-NH-propyldiamine', Journal of Coordination Chemistry, 60: 16, 1721 — 1729
To link to this Article: DOI: 10.1080/00958970601117365
URL: http://dx.doi.org/10.1080/00958970601117365

Journal of Coordination Chemistry
Vol. 60, No. 16, 15 August 2007, 1721–1729

Synthesis, structure and antimicrobial study of two copper(II) complexes derived from paeonol and *R*-NH-propyldiamine

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(*Received 17 February 2006; in final form 26 May 2006*)

Two new copper(II) complexes were synthesized from 2-hydroxyl-4-methoxyacetophone with *R*-NH–CH_2–CH_2–CH_2–NH_2 (for complex **1**, $R = H$; complex **2**, $R = C_6H_5$–CH_2–) in the presence of Cu^{2+}. Crystals of **1** were monoclinic, space group $P2_1/n$, with $a = 12.6408(10)$ Å, $b = 7.4063(6)$ Å, $c = 16.8863(14)$ Å and $\beta = 93.3590(10)^\circ$, complex **2** crystals were triclinic, space group $P\bar{1}$ with $a = 7.561(3)$ Å, $b = 10.680(4)$ Å, $c = 13.868(5)$ Å and $\alpha = 97.389(6)^\circ$, $\beta = 95.240(6)^\circ$, $\gamma = 101.206(6)^\circ$. Both Cu(II) atoms were four-coordinate with distorted square-planar geometry. The toxicity of **1** and **2** were evaluated by testing antimicrobial activity against bacterial strands.

Keywords: Copper (II) complex; Paeonol; Crystal structure; Toxicity

1. Introduction

Copper(II) complexes with dimaine ligands have been synthesized, but, paeonol-copper(II)-diamine have only been reported recently [1, 2]. Paeonol, 2-hydroxyl-4-methoxyacetophenone, is an effective component of many traditional Chinese medicines. In modern medicine paeonol has a variety of effects including: antibacteria, antiinflammation, relieving pain, antisensitive and strengthening the immune system [3–6]. Paeonol has attracted considerable attention because of their potential biological properties and catalytic activity [7, 8]. Pfeiffer studied its chelating properties with several metals, including copper(II), and stoichometries then reported (denoting paeonol as HP) included: CuP_2, $CuP_2 \cdot C_6H_5NH_2$ and $CuP_2 \cdot$ pyridine [9]. E. R. J. Sillanpaa described the formation and structure of bis-paeonoliminocopper(II) [10]. Recently, new metallic complexes of paeonol have been prepared and characterized, but few crystal structures have been reported on these complexes [11–14]. Here we report

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Journal of Coordination Chemistry
ISSN 0095-8972 print/ISSN 1029-0389 online © 2007 Taylor & Francis
DOI: 10.1080/00958970601117365

the synthesis, structural characterization and toxicity of two copper(II) complexes derived from paeonal and *R*-NH–CH_2–CH_2–CH_2–NH_2.

2. Experimental

2.1. *Materials and instrumentation*

All starting materials and solvents were of analytical purity. Elemental analyses were determined with a Perkin-Elmer 240°C instrument. IR spectra were measured as KBr discs using a Nicolet 5DX FT-IR spectrophotometer. ES mass spectral measurement of the complex was carried out on a LCQ System (Finngann MAT, USA) using methanol as the mobile phase.

2.2. *Preparation of N-benzyl-1,3-propyldiamine*

N-(2-nitrilethyl)benzylamine (0.625 M, 100 g), NaOH (0.500 M, 20 g) and Raney nickel (10 g) were dissolved in 800 mL of ethanol. The mixture was hydrogenated for 2 h under 2.5 MPa at 60°C, filtered and all solvents distilled under vacuum. The colorless oil product was obtained. Yield 63.4 g, 62%. b.p.: 196 ~ 197°C (−0.098 MPa). ^{1}H NMR (D_2O)δ: 1.37–1.46(2H, –$CH_2CH_2CH_2$–), 2.34–2.46(4H, 2 × CH_2), 2.20–2.22(H, –NH–), 3.50(2H, ϕ–CH_2–), 7.15–7.22(5H, ϕ–H); IR(cm^{-1}, KBr)ν: 3350, 3278(s, ν_{as}, $\nu_{s\ (NH_2)}$), 2938, 2851(m, ν_{as}, $\nu_{s(CH_2)}$), 1581(m, $\nu_{(NH)}$), 1454–1488(phenyl), MS *m*/*z* (%): 165.3, $M^+ + 1$(91).

2.3. *Preparation of metal complexes*

The title complexes were synthesized as follows: to a stirred solution of paeonol (0.166 g, 1 mM) and $Cu(ClO_4)_2 \cdot 6H_2O$ (0.372 g, 1 mM) in 25 cm^3 absolute methanol was added dropwise a solution of *R*-NH–CH_2–CH_2–CH_2–NH_2 (1 mM) in 10 cm^3 absolute methanol at 25°C. After stirring for 2 h at 45°C, the complexes precipitated and were filtered off, washed with methanol and dried in vacuo. Single crystals of **1** and **2** suitable for X-ray structure determination were obtained by slow evaporation of the resulting filtrates for two weeks at ambient temperature. Table 1 lists analytical data of the complexes.

Table 1. Analytical data for the complexes.

Complex (colour)	Yield (%)	M.p. (°C)	IR			Anal. found (Calcd) (%)		
			$\nu_{(NH)}$	$\nu_{(C=O)}$	$\nu_{(ClO_4)}$	C	H	N
1 (blue-purple)	78	216.5	3336 3301	1611	1019	35.78 (35.80)	4.68 (4.72)	6.91 (6.96)
2 (deep-green)	64	196.6 ~ 197.9	3232 3268	1628	1072	31.26 (46.30)	5.13 (5.08)	5.75 (5.69)

Caution: Perchlorate salts of metal complexes with organic ligands are potentially explosive. Only small amounts of material should be prepared, and these should be handled with caution.

2.4. *X-ray crystallography*

Suitable crystals of **1** and **2** were mounted on a glass fiber. The crystal data were collected at 293(2) K on a Bruker SMART/CCD area-detector diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods using SHELXL-97 and refined by full-matrix least squares calculation on F^2 using SHELXL-97 [15]. All H atoms were placed in calculated positions. Full-matrix least-squares were used to refine an overall scale factor, positional and thermal parameters. The details of data collection, refinement and crystallographic data are summarized in table 2.

2.5. *Antimicrobial activity determination*

Toxicity of the complexes was evaluated by testing antimicrobial activity to bacterial strands using the agar diffusion method as described in the literature [16].

Table 2. Crystal data, data collection and structure refinement parameters for **1** and **2**.

Complex	**1**	**2**
Empirical formula	$C_{12}H_{19}ClCuN_2O_7$	$C_{19}H_{25}ClCuN_2O_7$
Formula weight	402.28	492.40
Radiation (Å)	Mo-Kα, 0.71073	Mo-Kα, 0.71073
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/n$	$P\bar{1}$
a (Å)	12.6408(10)	7.561(3)
b (Å)	7.4063(6)	10.680(4)
c (Å)	16.8863(14)	13.868(5)
α (°)	90	97.389(6)
β (°)	93.3590(10)	95.240(6)
γ (°)	90	101.206(6)
V (Å^3)	1578.2(2)	1081.5(7)
Z	4	2
D_{Calcd} (Mg m^{-3})	1.693	1.512
Absorption coefficient (mm^{-1})	1.590	1.176
θ range (°)	1.96–27.89	1.49–27.88
Index ranges	$-16 \le h \le 16$, $0 \le k \le 9$, $0 \le l \le 22$	$-9 \le h \le 9$, $-13 \le k \le 14$, $-17 \le l \le 17$
Reflections collected	3617	9156
Independent reflections	3617 [$R_{int} = 0.0000$]	4754 [$R_{int} = 0.0218$]
Independent reflections ($>2\sigma$)	2924	4047
Absorption correction	Semi-empirical from equivalents	Semi-empirical equivalents
Max/min transmissions	0.7211 and 0.6919	0.8433 and 0.7193
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	3617/0/210	4754/0/277
Goodness-of-fit on F^2	1.036	1.068
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0432$, $wR_2 = 0.1088$	$R_1 = 0.0450$, $wR_2 = 0.1187$
R indices (all data)	$R_1 = 0.0558$, $wR_2 = 0.1146$	$R_1 = 0.0548$, $wR_2 = 0.1296$
Largest diff. peak and hole	0.629 and −0.513 e (Å^{-3})	0.553 and −0.481 e (Å^{-3})

Complexes dissolved in DMF were tested against standard strains of *Candida albicans* CMCC (F) 98,001, *Staphylococcus aureus* CMCC (B) 26,003, *Bacillus pumilus* CMCC (B) 63,202, *Bacillus coliforms* CMCC (B) 44,102. For comparison, the antimicrobial activity of paeonol and $Cu(ClO_4)_2 \cdot 6H_2O$ are also tested. Nutrient agar thawed by heating in a water bath was transferred to glass plates and frozen at 37°C. After test strains were spread on the solid nutrient agar surface, stainless steel tubes ($7.8 \times 6 \times 10$ mm) were placed vertically on the surface. 0.228 mL samples with certain concentration were injected to the steel tubes. They were allowed to incubate at 37°C for 24 h. The inhibition zone around the disc was calculated as zone diameter in millimeters. Blank tests showed that DMF in the preparation of the test solutions does not affect the test organisms. All tests were repeated three times and average data were taken as the final result.

3. Results and discussion

3.1. *Crystal structures*

The crystal structure of complex **1** consists of a cationic unit of $[CuL1]^+$ and a non-coordinated perchlorate ion. A perspective view of $[CuL1]^+$ is shown in figure 1(a), and selected bond lengths and bond angles relevant to the Cu coordination sphere are listed in table 3. Cu(II) is four-coordinated with closely planar coordination by two N atoms of 1,3-propyldiamine and two O atoms of paeonol. In a molecular unit, one hydrogen atom of hydroxyl of apaeonol was lost during formation of the bond. The bond lengths of Cu(1)–O(1) and Cu(1)–O(3), 1.9016(19) and 1.956(2) Å, respectively, are similar to previous report [10], but the bond lengths of Cu(1)–N(1) and Cu(1)–N(2), 1.989(2) and 1.990(2) Å, respectively, are somewhat longer than corresponding distances $[Cu(C_9H_9O_3)_2 \cdot 2H_2O]$ [10]. The six bond angles formed by Cu(1) and coordination atoms are 90.64(8), 87.07(9), 177.65(8), 177.68(9), 87.13(10) and 95.17(10)°, with little departure from a square-plane. The dihedral angle between chelating ring plane 1 (composed of atoms Cu(1), N(1), N(2), C(10), C(11) and C(12)) and chelating ring plane 2 (composed of atoms Cu(1), O(1), O(3), C(8), C(1) and C(2)) is 23.7°. The dihedral angle between the aromatic ring (composed of atoms C(1) to C(6)) and plane 2 is 8.8°, and therefore a approximately coplanar conjugation system was formed.

Complex **1** and **2** possesses a four-coordinate CuN_2O_2 environment also. Similar distorted square planar geometry of Cu ion in the cationic unit of complex 2 is observed. The perspective view of $[CuL2]^+$ is shown in figure 2(a); selected bond lengths and bond angles relevant to the Cu coordination sphere are listed in table 4. $[CuL2]^+$ is similar to $[CuL1]^+$ but with somewhat different bond lengths and angles. The dihedral angle between chelating ring plane 1 (composed of atoms Cu(1), N(1), N(2), C(17), C(18) and C(19)) and chelating ring plane 2 (composed of atoms Cu(1), O(1), O(3), C(1), C(2) and C(8)) is 30.5°. The dihedral angle between the aromatic ring (composed of atoms C(1) to (6)) and plane 2 is 4.5°, indicating approximately coplanar conjugation. Planes 2 and 4 (composed of C(10) ~ C(16) and N(1)) are approximately vertical with a dihedral angle of 103.3°. The difference between $[CuL2]^+$ and $[CuL1]^+$ may mainly be attributed to the substituting group.

Packing diagrams, figures 1(b) and 2(b), show that extensive hydrogen bonds occur in the structure of the complexes. Relevant hydrogen bond lengths and bond angles are

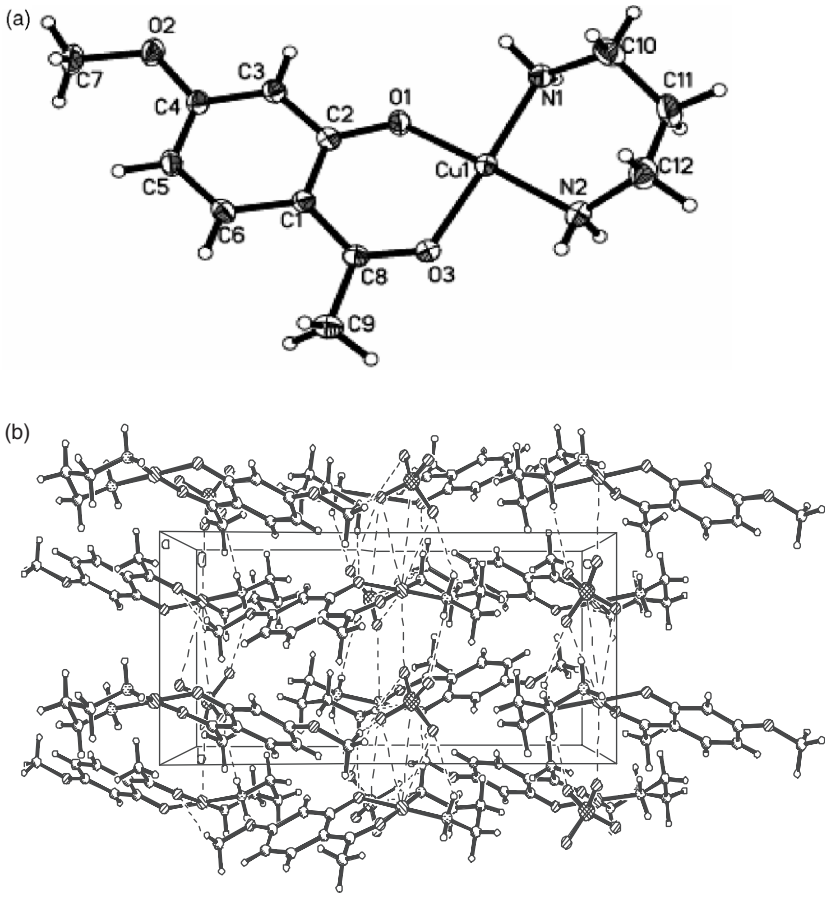

Figure 1. (a) Perspective view of the molecular structure for $[CuL1]^+$ (ellipsoids at 30% probability), (b) perspective view of crystal packing for **1** (ellipsoids at 30% probability).

Table 3. Selected bond distances (Å) and bond angles (°) for $[CuL1]^+$.

Cu(1)–O(1)	1.9016(19)	Cu(1)–O(3)	1.956(2)
Cu(1)–N(1)	1.989(2)	Cu(1)–N(2)	1.990(2)
C(2)–O(1)	1.314(3)	C(10)–N(1)	1.482(4)
N(1)–Cu(1)–N(2)	95.17(10)	O(1)–Cu(1)–O(3)	90.64(8)
O(1)–Cu(1)–N(1)	87.07(9)	O(3)–Cu(1)–N(1)	177.65(8)
O(1)–Cu(1)–N(2)	177.69(9)	O(3)–Cu(1)–N(2)	87.13(10)
C(12)–N(2)–Cu(1)	119.9(2)	C(2)–O(1)–Cu(1)	125.49(17)

given in table 5. Each perchlorate anion forms hydrogen bonds with an amino group of the adjacent complex cation. For the two complexes, intermolecular hydrogen bonds and intermolecular van der Waals interactions produced a three-dimensional framework and stabilized the crystal structure.

Bond distance and bond angle changes to paeonol in different complexes are shown in table 6. There is little difference between $[CuL1]^+$ and $[CuL2]^+$, but there are some

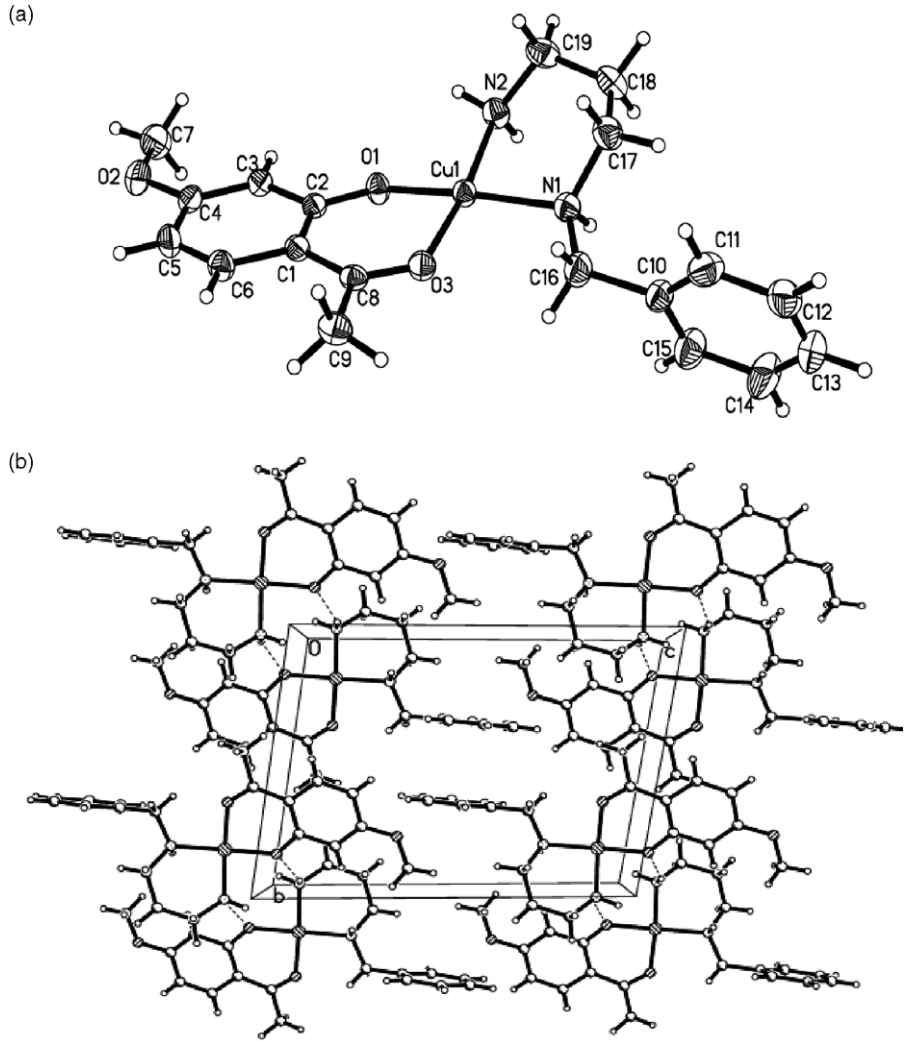

Figure 2. (a) Perspective view of the molecular structure for $[CuL_2]^+$ (ellipsoids at 30% probability), (b) perspective view of crystal packing for **2** (ellipsoids at 30% probability).

differences between $Cu(C_9H_9O_3)_2 \cdot 2H_2O$ [10] and **1** and **2** may be attributed to the influence of Schiff base of $Cu(C_9H_9O_3)_2 \cdot 2H_2O$.

3.2. *Spectral characteristics*

The IR spectra of both complexes are similar, indicating a similar structural relationship (see table 1). Incomplete condensation of primary amine groups and carbonyl groups is confirmed by the lack of C=N stretching bands in the IR region 1640–1650 cm^{-1} and the presence of strong N–H stretching bands at 3200–3340 cm^{-1}. The ν(O–H) band originally found in paeonol disappeared on complexation indicating

Table 4. Selected bond distances (Å) and bond angles (°) for $[CuL2]^+$.

Cu(1)–O(1)	1.909(2)	Cu(1)–O(3)	1.931(2)
Cu(1)–N(2)	1.990(2)	Cu(1)–N(1)	2.043(3)
C(2)–O(1)	1.306(3)	C(4)–O(2)	1.358(4)
C(18)–C(19)	1.498(5)	C(19)–N(2)	1.466(4)
O(1)–Cu(1)–O(3)	90.66(8)	O(1)–Cu(1)–N(2)	85.86(9)
O(3)–Cu(1)–N(2)	172.23(10)	O(1)–Cu(1)–N(1)	171.35(10)
O(3)–Cu(1)–N(1)	92.35(10)	N(2)–Cu(1)–N(1)	92.09(10)

Table 5. Hydrogen bond geometries (Å, °).

Complex	D–H···A	d_{D-H}	$d_{H\cdots A}$	$d_{D\cdots A}$	θ_{DHA}
1	N(1)–H(1A)···O(1)	0.90	2.26	3.053(3)	147.6
	N(1)–H(1B)···O(6)	0.90	2.28	3.139(3)	159.6
	N(2)–H(2A)···O(4)	0.90	2.39	3.159(4)	143.5
	N(2)–H(2B)···O(7)	0.90	2.44	3.028(4)	123.2
	N(2)–H(2B)···O(2)	0.90	2.63	3.142(3)	117.2
2	N(2)–H(2A)···O(1)	0.90	2.31	3.124(3)	150.1
	N(2)–H(2B)···O(5)	0.90	2.38	3.144(4)	142.3
	N(2)–H(2B)···O(6)	0.90	2.63	3.453(4)	153.2
	N(1)–H(1)···O(4)	0.94	2.33	3.230	161.0(4)

Table 6. Selected bond distances (Å) and bond angles (°) for paeonol in complexes.

Compound	C(2)–O(1)	C(4)–O(2)	C(8)–O(3)	C(2)–C(1)–O(1)	C(4)–O(2)–C(7)
Paeonol [12]	1.345(2)	1.355(3)	1.232(3)	122.0(2)	117.94(19)
$Cu(C_9H_9O_3)_2 \cdot 2H_2O$ [10]	1.30(1)	1.35(1)	–	–	116.7(7)
$[CuL1]ClO_4$	1.314(4)	1.364(3)	1.258(3)	124.1(2)	118.0(2)
$[CuL2]ClO_4$	1.306(3)	1.359(4)	1.256(3)	124.1(3)	118.8(3)

deprotonation of the phenolic hydroxyl group and coordination of phenolic oxygen to the metal ion. The strong peaks at 1072–1080 cm^{-1} without splitting show that ClO_4^- does not coordinate with Cu atoms.

3.3. *Antimicrobial activity*

Paeonol, $Cu(ClO_4)_2 \cdot 6H_2O$ and both complexes were active against four test organisms, showing similar antimicrobial activities (see table 7). The highest antimicrobial activity among these organisms was observed against *C. albicans*. In the range of 16.6–2.0 mg mL^{-1}, these compounds were more active against the test strains with increase of concentration. The metal salt $Cu(ClO_4)_2 \cdot 6H_2O$ shows higher activity against bacteria as compared to the two complexes and paeonol, indicating that the metal center is an essential factor to the antibacterial value. From the data in table 6, the two complexes show higher activity against bacteria as compared to paeonol. The different substituting group has little influence on antimicrobial activity, but small

Table 7. The diameter of inhibition zone (mm).

Compound	Concentration ($mg\,mL^{-1}$)	Diameter of inhibition zone (mm)			
		C. albicans	*S. aureus*	*B. pumilus*	*B. coliforms*
Paeonol	16.6	31.38	20.40	22.18	24.94
	8.3	28.74	16.42	21.88	21.62
	4.1	22.12	14.68	20.16	16.86
	2.0	21.38	14.46	15.42	16.64
$[CuL1]\cdot ClO_4$	16.6	38.36	22.68	28.12	26.32
	8.3	33.92	16.80	26.38	25.54
	4.1	26.14	15.84	22.94	23.14
	2.0	26.10	15.26	22.42	23.08
$[CuL2]\cdot ClO_4$	16.6	37.62	26.72	27.38	27.48
	8.3	33.90	18.94	26.42	27.36
	4.1	20.86	17.68	25.66	26.64
	2.0	20.44	16.36	25.08	26.08
$Cu(ClO_4)_2\cdot 6H_2O$	16.6	39.78	30.18	28.96	29.12
	8.3	37.60	28.46	28.12	27.64
	4.1	26.76	27.42	26.48	26.26
	2.0	25.43.	21.82	26.02	25.88

differences in toxicity between $[CuL1]\cdot ClO_4$ and $[CuL2]\cdot ClO_4$ were observed, mainly due to different structures.

Supplementary material

Crystallographic data for the structures in this article have been deposited with the Cambridge Crystallographic Data Center as the supplementary publication Nos. CCDC 608546 and 608547 for the complex **1** and the complex **2**, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

Acknowledgements

This work was supported by the Key Laboratory of Marine Biotechnology of Jiangsu Province.

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