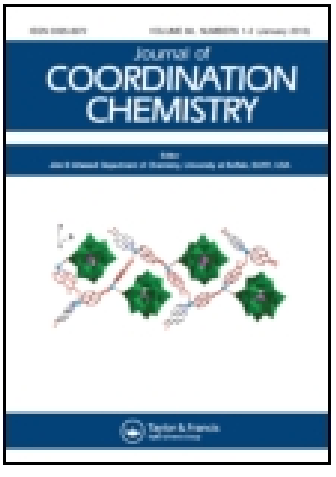

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Two Cu(II) complexes from an N-alkylated benzimidazole: synthesis, structural characterization, and biological properties

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Two Cu(II) complexes from an N-alkylated benzimidazole: synthesis, structural characterization, and biological properties

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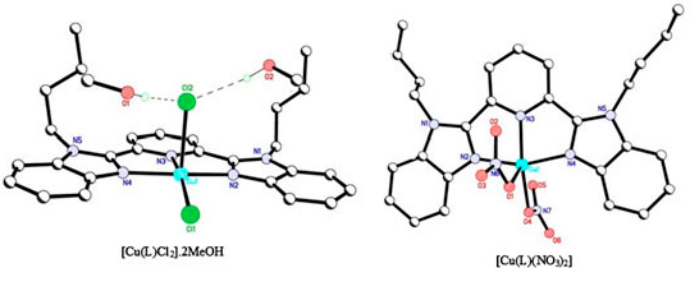

Two mononuclear copper(II) complexes, $[Cu(L)Cl_2](CH_3OH)_2$ and $[Cu(L)(NO_3)_2]$, were prepared and characterized by spectroscopic and analytic methods, where L is 2,6-bis(1-butyl-1*H*-benzo[*d*] imidazol-2-yl)pyridine. Molecular structures of the complexes were determined by X-ray diffraction. The X-ray data revealed that the complexes are mononuclear and coordination geometry around Cu(II) is distorted square pyramidal. The complexes were screened for their *in vitro* antibacterial and antifungal activities. The complexes show moderate antifungal activities against *Saccharomyces cerevisiae*, *Candida utilis,* and *Candida albicans*. Moreover, the complexes inhibit the development of *Escherichia coli* and *Klebsiella pneumoniae*.

Keywords: Cu(II) complex; Structural characterization; Benzimidazole; Antibacterial; Antifungal

1. Introduction

Imidazole and its derivatives are special ligands due to their prominent role in biological chemistry [1–3]. This class of compounds has been extensively used in inorganic chemistry and biological applications [4, 5]. Benzimidazole is a hetero-bicyclic aromatic organic compound which contains the fusion of benzene and imidazole rings [6]. Benzimidazoles are found in a variety of biological processes [7]. *N*-ribosyl-dimethylbenzimidazole, for

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example, is a benzimidazole found in vitamin B12 and serves as an axial ligand for cobalt [8]. Benzimidazole derivatives are of interest due to their remarkable biological activity and clinical applications [9, 10]. Some benzimidazoles have antiviral, antibacterial, antifungal, antimalarial, and anthelmintic activities [10–13]. Several benzimidazole derivatives were synthesized by derivatization at N–H [14–16]. Transition metal complexes of these ligands have been studied as potential metallodrugs and as models of some biological molecules [17].

Transition metal complexes of 2,2′-pyridine-2,6-diylbis(1H-benzimidazole) (bzimpy) (figure 1) were synthesized and their properties were extensively investigated [18–23]. The biological activity and pharmacological properties of the benzimidazole derivatives have led us to investigate the coordination behavior of benzimidazole ligands towards transition metal ions. Herein, an *N*-butylalkylated benzimidazole and two Cu(II) complexes were prepared and characterized by analytical and spectroscopic methods. Antimicrobial activity of the complexes was investigated.

2. Experimental

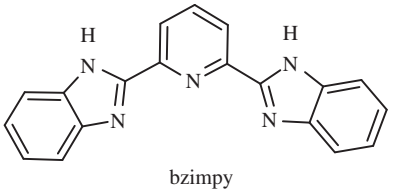
2.1. *General methods*

All starting materials and solvents were purchased from commercial sources and used as received, unless otherwise noted. IR spectra were performed using KBr pellets on a Perkin Elmer Paragon 1000PC. CHN analyses were performed using a CE-440 Elemental Analyzer. ^{1}H and ^{13}C NMR spectra were performed using a Bruker Avance 400. Mass spectra were recorded on a Thermo Fisher Exactive + Triversa Nanomate mass spectrometer. Electronic spectra from 200 to 900 nm were obtained on a Shimadzu UV-1800 UV–vis spectrophotometer.

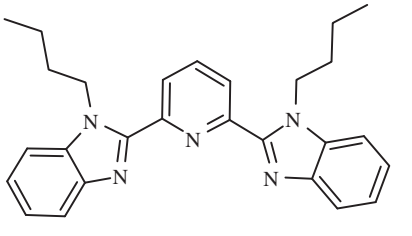
Data collection and cell refinement for X-ray crystallography were completed using a Bruker APEX2 CCD diffractometer and data reduction was performed using Bruker SAINT. SHELXTL was used to solve and refine the structures [24].

2.2. *X-ray structures solution and refinement for the complexes*

X-ray diffraction data were collected at 150(2) K on a Bruker APEX2 CCD diffractometer using Mo Kα radiation ($\gamma = 0.71073$ Å). The structure was solved by direct methods and refined on F^2 using all reflections [25]. All non-hydrogen atoms were refined using



bzimpy



L

Figure 1. Benzimidazole ligand L.

Table 1. Crystallographic data.

Complex	$[Cu(L)Cl_2]\cdot 2MeOH$	$[Cu(L)(NO_3)_2]$
Empirical formula	$C_{29}H_{37}Cl_2CuN_5O_2$	$C_{27}H_{29}CuN_7O_6$
Formula weight	622.08	611.11
Crystal system	*Monoclinic*	*Monoclinic*
Space group	$P2_1/n$	$P2_1/n$
Unit cell dimensions		
a (Å)	8.5601(4)	8.5066(3)
b (Å)	25.4439(11)	15.8171(6)
c (Å)	13.4674(6)	20.5026(8)
α (°)	90	90
β (°)	91.3360(10)	97.0420(10)
γ (°)	90	90
Volume (Å^3)	2932.4(2)	2737.81(18)
Z	4	4
Abs. coeff. (mm^{-1})	0.962	0.853
Refl. collected	29,912	23,973
Ind. refl. [R_{int}]	7310 [0.0240]	5623 [0.0200]
R_1, wR_2 [$I > 2\sigma(I)$]	0.0272, 0.0698	0.0263, 0.0716
R_1, wR_2 (all data)	0.0331, 0.0733	0.0310, 0.0744
CCDC	984502	984503

Table 2. Selected bond lengths [Å] and angles [°] for $[Cu(L)Cl_2]\cdot 2MeOH$.

Cu(1)–N(3)	1.9901(11)	Cu(1)–Cl(1)	2.2198(4)
Cu(1)–N(2)	2.0160(12)	Cu(1)–Cl(2)	2.6003(4)
Cu(1)–N(4)	2.0094(12)		
N(3)–Cu(1)–N(4)	79.25(5)	N(3)–Cu(1)–N(2)	79.15(5)
N(4)–Cu(1)–N(2)	157.46(5)	N(3)–Cu(1)–Cl(1)	163.77(4)
N(4)–Cu(1)–Cl(1)	99.26(3)	N(2)–Cu(1)–Cl(1)	99.67(3)
N(3)–Cu(1)–Cl(2)	88.84(3)	N(4)–Cu(1)–Cl(2)	92.75(3)
N(2)–Cu(1)–Cl(2)	93.18(4)	Cl(1)–Cu(1)–Cl(2)	107.387(14)

anisotropic atomic displacement parameters and hydrogens were inserted at calculated positions using a riding model. In $[Cu(L)Cl_2]\cdot 2MeOH$, hydrogens bonded to MeOH were located from difference maps and refined with temperature factors, riding on the carrier atom. Details of the crystal data and refinement are given in table 1. Selected bond lengths and angles for $[Cu(L)Cl_2]\cdot 2MeOH$ and $[Cu(L)(NO_3)_2]$ are given in tables 2 and 4.

2.3. *Synthesis of 2,6-bis-(benzimidazol-2-yl)-pyridine (bzimpy)*

2,6-Bis-(benzimidazol-2-yl)-pyridine (bzimpy) was synthesized according to the published method [26]. Yield: 68%. Colorless NMR: (DMSO as solvent, ppm, ^{1}H) 7.31 (*t*, 4H, CH aromatic), 7.76 (*d* 4H CH aromatic), 8.16 (*t* 1H CH aromatic), 8.34 (*d* 1H CH aromatic). IR: 3193, 1601, 1573, 1318, 1278, 1230, 819, 738 cm^{-1}. Mass spect. (ESI): *m/z* 312 $[L + H]^+$ (100%), 334 $[L + Na]^+$ (30%).

2.4. *2,6-Bis(1-butyl-1H-benzo[d]imidazol-2-yl)pyridine (L)*

N-butylation of 2,6-bis(benzimidazol-2′-yl)pyridine (bzimpy) was prepared by a reported general N-alkylation method [27]. Bzimpy (1.00 g, 3.2 mM) and NaOH (0.50 g, 12.8 mM)

were stirred overnight at 60 °C. To the stirring solution, 1-bromobutane (1.30 g, 9.6 mM) was added and stirred for two days at 60 °C. The solvent was then removed on a rotary evaporator to give a white–yellow residue. Chloroform (20 mL) was added to the residue and the precipitated NaBr was removed by filtration. Evaporation of the chloroform yielded a creamy product.

Yield: 1.05 g, 78% (based on bzimpy). Elemental analysis data: Anal. (%) Calcd for $C_{27}H_{29}N_5$ (423.55): C, 76.56; H, 6.90; N, 16.53. Found (%): C, 76.28; H, 6.65; N, 16.37. ^{1}H NMR: ($CDCl_3$ as solvent, ppm), 0.71 (*t* 6H CH_3–C), 1.35 (*s* (*sextet*) 4H C–CH_2–C), 4.73 (*t* 4H C–CH_2–C), 1.72 (*q (quintet)* 4H C–CH_2–), 7.37–7.47 (*t* 4H CH aromatic), 7.89 (*d* 4H CH aromatic), 8.06 (*t* 1H CH aromatic), 8.33 (*d* 1H CH aromatic). ^{13}C NMR ($CDCl_3$-d_6 as solvent, ppm): 13.48, 19.85, 32.12, 44.64 (aliphatic), 110.39, 120.34, 122.71, 123.47, 125.50, 136.31, 138.11, 142.86, 150.57 (aromatic). IR (KBr, *v*, cm^{-1}): 2956, 2929, 2871, 1434, 1410, 1571, 1328, 1285, 1249, 1178, 1076, 993, 823, 740, 660, 581 cm^{-1}. Mass spect. (ESI): *m/z* 424 $[L]H^+$ (100%), 446 $[L]Na^+$ (25%), 847 $[(L)_2 + H]^+$ (40%), 869 $[(L)_2 + Na]^+$ (25%).

2.5. *Preparation of the complexes*

2.5.1. $[Cu(L)Cl_2]\cdot 2CH_3OH$. $CuCl_2\cdot 2H_2O$ (0.31 g, 1.77 mM) was added to a refluxing solution of L (0.75 g, 1.77 mM) in MeOH (50 mL). When the addition was completed, the green solution was further refluxed for 4 h then cooled to room temperature. Large crystals formed in a few days were collected and dried in air. Yield: 0.85 g, 77% (based on copper salt). Color: green. m.p. 312–320 °C. Elemental analysis data: Anal. (%) Calcd for $C_{29}H_{37}Cl_2CuN_5O_2$ (622.08): C, 55.99; H, 5.99; N, 11.26. Found (%): C, 55.63; H, 5.70; N, 11.02. IR (KBr, *v*, cm^{-1}): 2951, 2872, 2867, 1598, 1508, 1480, 1460, 1442, 1334, 1157, 1133, 1055, 1033, 1007, 926, 867, 804, 749, 690, 621, 491, 481, 469, 436, 398 cm^{-1}. Mass spect. (ESI): *m/z* 987(2%) $[Cu(L)_2]Cl\cdot(CH_3OH)^+$, 944(2%) $[Cu(L)_2]Cl^+$, 521(100%) $[Cu(L)Cl]^+$, 486(10%) $[Cu(L)]^+$, 454(5%) $[Cu(L)_2]^{2+}$.

2.5.2. $[Cu(L)(NO_3)_2]$. $Cu(NO_3)_2\cdot 3H_2O$ (0.43 g, 1.77 mM) was added to a refluxing solution of L (0.75 g, 1.77 mM) in MeOH (50 mL). When the addition was completed, the green solution was further refluxed for 4 h then cooled to room temperature. The complex was obtained as crystals from the solution mixture. Green crystals were collected, washed with diethyl ether and dried in air.

Yield: 0.92 g, 85%. Color: green. m.p. 320–330 °C. Elemental analysis data: Anal. (%) Calcd for $C_{27}H_{29}CuN_7O_6$ (611.11): C, 53.21; H, 4.78; N, 16.04. Found (%): C, 53.07; H, 4.21; N, 15.43. IR (KBr, *v*, cm^{-1}): 2958, 2871, 2869, 1606, 1511, 1475, 1435, 1328, 1295, 1198, 1156, 1086, 1020, 926, 865, 806, 746, 676, 642, 492, 460, 431, 398 cm^{-1}. Mass spect. (ESI): *m/z* 548(35%) $[Cu(L)(NO_3)]^+$, 517(35%) $[Cu(L)](CH_3OH)^+$, 503(70%) $[Cu(L)](H_2O)^+$, 486(100%) $[Cu(L)]^+$.

2.6. *Biological properties*

The antimicrobial activities of the complexes were tested against five bacteria [*Bacillus subtilis* IMG22, *Bacillus cereus* EU, *Klebsiella pneumoniae* FMC *5*, *Escherichia coli* DM, and *Enterobacter aerogenes* (Clinic izolate)] and three yeasts (*Candida albicans* ATCC

1023, *Candida utilis* NRRL-Y-900, and *Saccharomyces cerevisiae* WET 136). These micro-organisms were provided from Microbiology Laboratory Culture Collection, Department of Biology, Kahramanmaraş Sütçü İmam University, Turkey.

Antimicrobial activities of the complexes were determined using the hollow agar, as described below. The bacteria were first incubated at 37 ± 0.1 °C for 24 h in nutrient broth (Difco), and the yeasts were incubated in sabouraud dextrose broth (Difco) at 25 ± 0.1 °C for 24 h. The cultures of the bacteria and yeast were injected into Petri dishes (9 cm) in the amount of 0.1 mL (Mc Farland OD: 0.5, 1.5×10^8 bacteria mL^{-1} and 1.5×10^6 yeast mL^{-1}). Then, Mueller Hinton agar and sabouraud dextrose agar (sterilized in a flask and cooled to 45–50 °C) were homogeneously distributed onto the sterilized Petri dishes in the amount of 25 mL. Subsequently, complex solutions (700 µL) in MeOH were pipetted into the hollow agar. In addition, blank paper disks treated with antibacterial ampicillin (10 µg) and antifungal nystatin 100U were used as positive controls. Afterward, the plates combined with the disks were left at 4 °C for 2 h, the plates injected with yeast were incubated at 25 ± 0.1 °C for 24 h, and the ones injected with bacteria were incubated at 37 ± 0.1 °C for 24 h. After 24 h, inhibition zones appearing around the disks were measured and recorded in mm [28, 29].

2.7. *Determination of minimal inhibitory concentration*

A broth microdilution broth susceptibility assay was used, as recommended by NCCLS, for the determination of the Minimal inhibitory concentrations (MIC) of the complexes. All tests were performed in Mueller Hinton broth (MHB) supplemented with Tween 80 detergent (final concentration of 0.5% (v/v)), with the exception of the yeasts (sabouraud dextrose broth (SDB) + Tween 80). Bacterial strains were cultured overnight at 37 °C in MHB, and the yeasts were cultured overnight at 25 °C in SDB. Geometric dilutions ranging from 100 to 800 µg mL^{-1} of the complexes were prepared including one growth control (MHB + Tween 80) and one sterility control (MHB + Tween 80 + test oil). Test tubes were incubated under normal atmospheric conditions at 37 °C for 24 h for bacteria and at 25 °C for 48 h for the yeasts. The microbial growth was determined by turbidimetric methods.

3. Results and discussion

The ligand 2,6-bis(1-butyl-1H-benzo[d]imidazol-2-yl)pyridine (L) was obtained as sticky cream oil by the reaction of 2,6-bis-(benzimidazol-2-yl)-pyridine (bzimpy) and 1-bromobutane in the presence of a base (NaOH). The ^{1}H- and ^{13}C NMR spectra of L are presented in figures S1 and S2, see online supplemental material at http://dx.doi.org/10.1080/00958972.2014.920502, respectively. In the ^{1}H NMR spectrum, aromatic ring protons were at δ 7.28–8.02 ppm as multiplets. A doublet at δ 8.33 ppm and a triplet at δ 8.06 ppm in 2 : 1 ratio were assigned to pyridine protons. Benzene ring protons were seen at δ 7.28–7.89 ppm. Aliphatic protons were observed at δ 0.71–4.73 as multiplets. In the ^{13}C NMR spectrum of the ligand, aliphatic C shifts were observed between δ 13.48–44.64 ppm. All aromatic carbon shifts were observed at δ 110.39–150.57 ppm. Both ^{1}H and ^{13}C NMR spectra confirmed that there was no significant organic impurity in the sample.

Reactions of Cu(II) with L in the presence of Cl^- and NO_3^- in MeOH yield 1 : 1 (metal : ligand ratio) complexes. Both complexes are air-stable at room temperature without decomposition and are soluble in MeOH, EtOH, acetone, acetonitrile, DMF, and DMSO, slightly

soluble in chloroform and dichloromethane, and not soluble in water or diethyl ether. The elemental analysis data are in agreement with the calculated values.

In ESI, mass spectra of the complexes were recorded in MeOH and the data are given in Section 2. The ESI spectrum of $[Cu(L)Cl_2]\cdot 2CH_3OH$ is shown in figure 2. In the mass spectra of $[Cu(L)Cl_2]\cdot 2CH_3OH$, two peaks at *m/z* 521(100%) and 486(25%) were assigned to $[Cu(L)Cl]^+$ and $[Cu(L)]^+$, respectively. In the mass spectra of $[Cu(L)(NO_3)_2]$, signals with high relative abundance at 548(35%), 517(35%), 503(70%), and 486(100%) were assigned to $[Cu(L)(NO_3)]^+$, $[Cu(L)](CH_3OH)^+$, $[Cu(L)](H_2O)^+$, and $[Cu(L)]^+$, respectively.

The important IR data of the complexes are listed in Section 2. The new bands at 425–310 cm^{-1} in spectra of all complexes are assigned to ν(Cu–N). In the IR spectrum of $[Cu(L)(NO_3)_2]$, nitrate stretches were observed at 1475, 1295, and 1020 cm^{-1}. These three stretches show that at least one nitrate coordinates to copper. X-ray structure analysis showed that both nitrates are monodentate ligands.

The UV–vis absorption spectra of the complexes were investigated from 200 to 800 nm in MeOH (2×10^{-5} M). The absorption spectra (figure 3) are similar. The complexes show a maximum absorption at 260–340 nm assigned to $\pi \rightarrow \pi^*$ transitions of the aromatic rings. The absorption bands at 350–370 nm were assigned to $n \rightarrow \pi^*$ transition. In both complexes, there is also an absorption as a shoulder at 370–400 nm, assigned to M → L charge transition. The d–d transitions were not observed for both complexes.

3.1. *X-ray structure of $[Cu(L)Cl_2]\cdot 2MeOH$ and $[Cu(L)(NO_3)_2]$*

Molecular structures of $[Cu(L)Cl_2]\cdot 2MeOH$ and $[Cu(L)(NO_3)_2]$ with atom numbering are shown in figures 4 and 5. Both complexes crystallize in the monoclinic crystal system, $P2_1/n$ space group. Molecular structures of $[Cu(L)Cl_2]\cdot 2MeOH$ and $[Cu(L)(NO_3)_2]$ are similar. Both complexes contain a mononuclear five-coordinate Cu(II). The coordination sphere of Cu(II) in $[Cu(L)Cl_2]\cdot 2MeOH$ comprises three nitrogens from the tridentate ligand and two

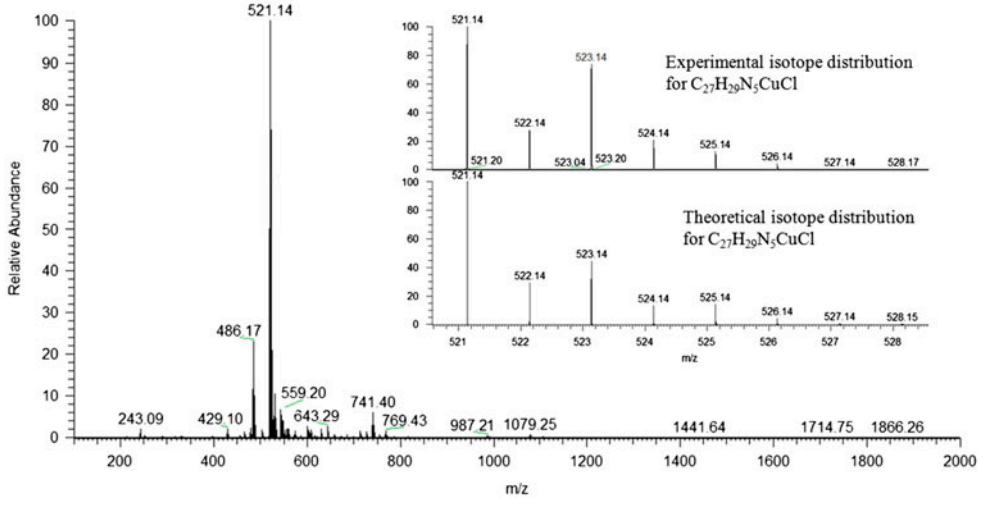


Figure 2. SI mass spectrum of $[Cu(L)Cl_2]\cdot 2CH_3OH$.

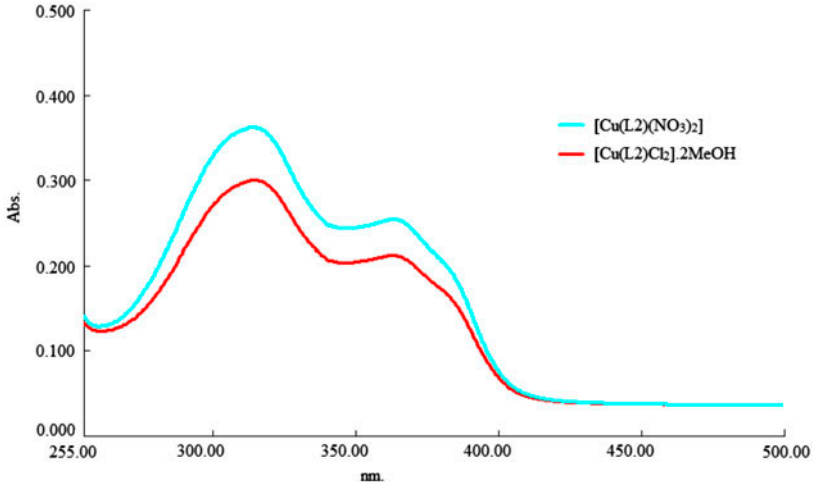


Figure 3. UV–vis spectra of complexes in MeOH (2×10^{-5} M).

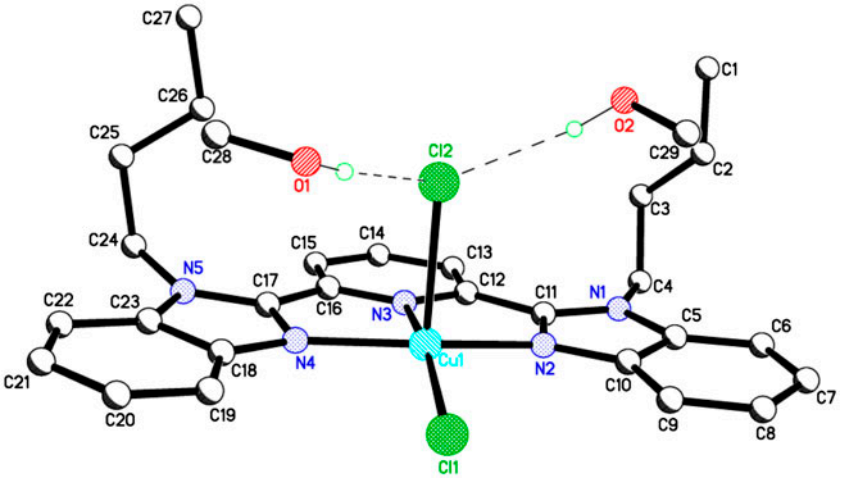


Figure 4. Perspective view of $[Cu(L)Cl_2]\cdot 2MeOH$ with atom labeling; hydrogens bonded to carbon are omitted for clarity.

chlorides (Cl1, Cl2); two chlorides are replaced by two oxygens of two nitrates in $[Cu(L)(NO_3)_2]$.

A geometry parameter τ, which is defined $\tau = (\beta - \alpha)/60$ where β and α are the two largest angles ($\beta > \alpha$), provides a measure of the degree of square pyramidal (SP) *versus* trigonal bipyramidal geometry. For an ideal square pyramid, τ is zero and for an ideal trigonal bipyramid, τ is 1.0 [30]. In $[Cu(L)Cl_2]\cdot 2MeOH$, the largest angles within N2, N3, N4, Cl1 are $\beta = 163.77°$ for N2–Cu1–N4, and $\alpha = 157.46°$ for N3–Cu1–Cl1. Thus, τ is (163.77–157.46)/60 = 0.105. This indicates that the geometry around Cu(II) is distorted SP. Three nitrogens (one pyridyl (N3) and two imidazole (N2, N4)) and one chloride (Cl1) are located in the

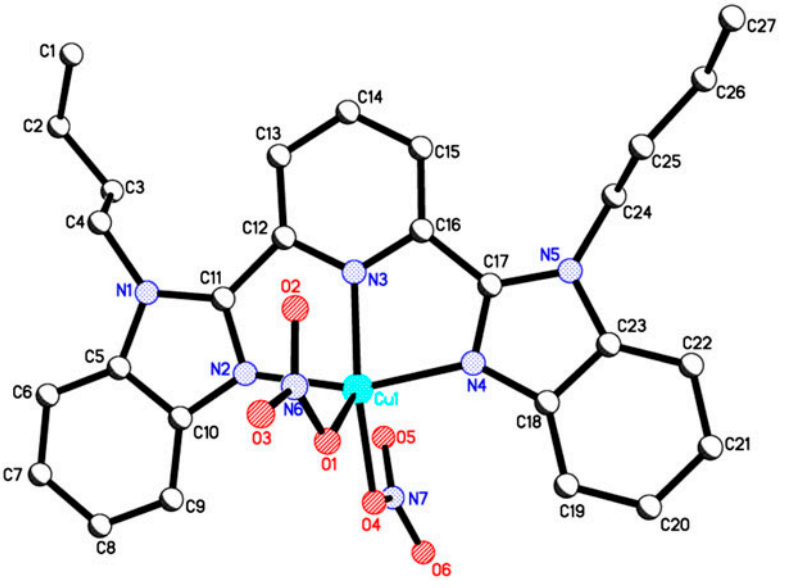


Figure 5. Molecular structure of $[Cu(L)(NO_3)_2]$ with atom numbering; hydrogens are omitted for clarity.

equatorial plane and a chloride (Cl2) is located axial. Cu–Cl(2) distance of 2.6003(4) Å is remarkably longer than those of Cu–N and Cu–Cl(1) distances at the equatorial position (table 2). Cl(2) involves hydrogen bonding with two MeOH molecules (figure 4 and table 3).

Geometry around Cu(II) in $[Cu(L)(NO_3)_2]$ is also slightly distorted SP. Three nitrogens (one pyridyl (N3) and two imidazole (N2, N4)) and an oxygen of nitrate (O4) are equatorial and O1 of nitrate is axial. In $[Cu(L)(NO_3)_2]$, the τ value is (159.03–157.68)/60 = 0.023. The Cu–O(4) distance (2.0153(11) Å) is shorter than that of Cu–O(1) bond distance (2.1895(11) Å) (table 4). Moreover, there is weak coordination between copper and O(5) and O(2) with distances of 2.634 and 2.940 Å, respectively, dramatically longer than those of usual Cu–O bond distances; therefore, the two nitrate anions can be considered monodentate.

In $[Cu(L)Cl_2]\cdot 2MeOH$, two butyl chains in the ligand are located below the equatorial plane which allows π–π interactions between the complex molecules. The pyridine ring of one complex is stacked with the benzene ring of the neighboring complex under symmetry operation of $1-x$, $-y$, $1-z$ (figure 6); C16 and C19 are separated by 3.363 Å (figure 6). Molecular packing of the complex is shown in figure 7.

In $[Cu(L)(NO_3)_2]$, there are two sets of π–π stacking interactions in the structure. One benzene (C18–C23) is stacked with the same section of the neighboring molecule (symmetry operation: $2-x$, $1-y$, $-z$); C(18) and C(22) are separated by a distance of 3.411 Å. In

Table 3. Hydrogen bond information for $[Cu(L)Cl_2]\cdot 2MeOH$ [Å and °].

D–H···A	d(D–H)	d(H···A)	d(D···A)	∠(DHA)
O(1)–H(1)···Cl(2)	0.88	2.25	3.1232(14)	174.8
O(2)–H(2)···Cl(2)	0.89	2.27	3.1455(15)	167.3

Table 4. Bond lengths [Å] and angles [°] for $[Cu(L)(NO_3)_2]$.

Cu(1)–N(2)	1.9788(12)	Cu(1)–N(3)	1.9805(12)
Cu(1)–N(4)	1.9861(12)	Cu(1)–O(4)	2.0153(11)
Cu(1)–O(1)	2.1895(11)		
N(2)–Cu(1)–N(3)	79.45(5)	N(2)–Cu(1)–N(4)	159.03(5)
N(3)–Cu(1)–N(4)	79.93(5)	N(2)–Cu(1)–O(4)	101.48(5)
N(3)–Cu(1)–O(4)	157.68(5)	N(4)–Cu(1)–O(4)	96.15(5)
N(2)–Cu(1)–O(1)	93.25(5)	N(3)–Cu(1)–O(1)	116.84(5)
N(4)–Cu(1)–O(1)	99.41(5)	O(4)–Cu(1)–O(1)	85.45(4)

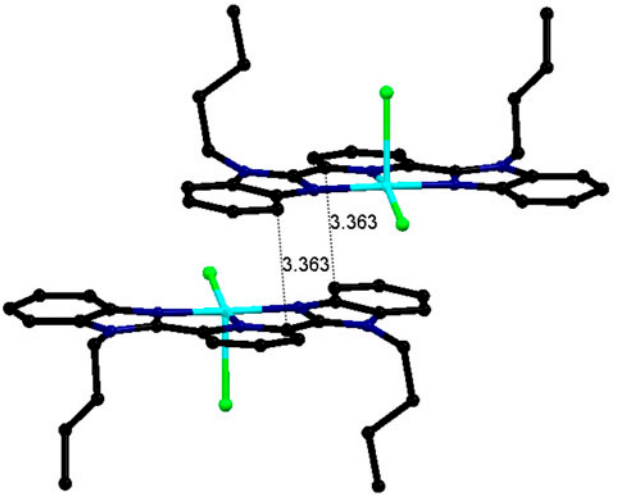


Figure 6. π–π interactions within the structure of $[Cu(L)Cl_2]\cdot 2MeOH$; hydrogens are omitted for clarity.

addition, C(14) of pyridine is stacked with C(9) of the benzene ring of the adjacent molecule with a distance of 3.482 Å (symmetry code: $1+x, y, z$) (figure 8). Molecular packing of the complex is determined by π–π and C–H(aromatic)···O weak hydrogen bond-type interactions shown in figure 9.

It is informative to compare crystal structures of $[Cu(L)Cl_2]\cdot 2MeOH$ and $[Cu(L)(NO_3)_2]$ with Cu(II) complexes of 2,6-bis-(benzimidazol-2-yl)-pyridine (bzimpy) in the presence of chloride and nitrate. $[Cu(bzimpy)Cl_2]\cdot DMF$ and $[Cu(bzimpy)(H_2O)_2](NO_3)_2$ were synthesized and structurally characterized by Bernardinelli *et al.* and Dey *et al.*, respectively (figure 10) [31, 32]. In $[Cu(L)Cl_2]\cdot 2MeOH$ and $[Cu(bzimpy)Cl_2]\cdot DMF$, Cu(II) ions are five-coordinate with distorted SP geometry and both have similar Cu-donor distances. In the published structure $[Cu(bzimpy)Cl_2]\cdot DMF$, three nitrogens of bzimpy and a chloride are coordinated to Cu(II) at the basal plane and a chloride at the axial position. In the published nitro complex $[Cu(bzimpy)(H_2O)_2](NO_3)_2$, Cu(II) ions are also five-coordinate with distorted SP geometry [32]. In $[Cu(L)(NO_3)_2]$, both nitrates coordinate monodentate to Cu(II); however, in $[Cu(bzimpy)(H_2O)_2](NO_3)_2$, both nitrates are not involved in coordination with Cu(II). In $[Cu(bzimpy)(H_2O)_2](NO_3)_2$, nitrates are involved in hydrogen bonding with NH (imidazole) groups and coordinated water, resulting in a 3-D hydrogen-bonding network. Coordination geometry around Cu(II) in the published structure $[Cu(bzimpy)(H_2O)_2](NO_3)_2$

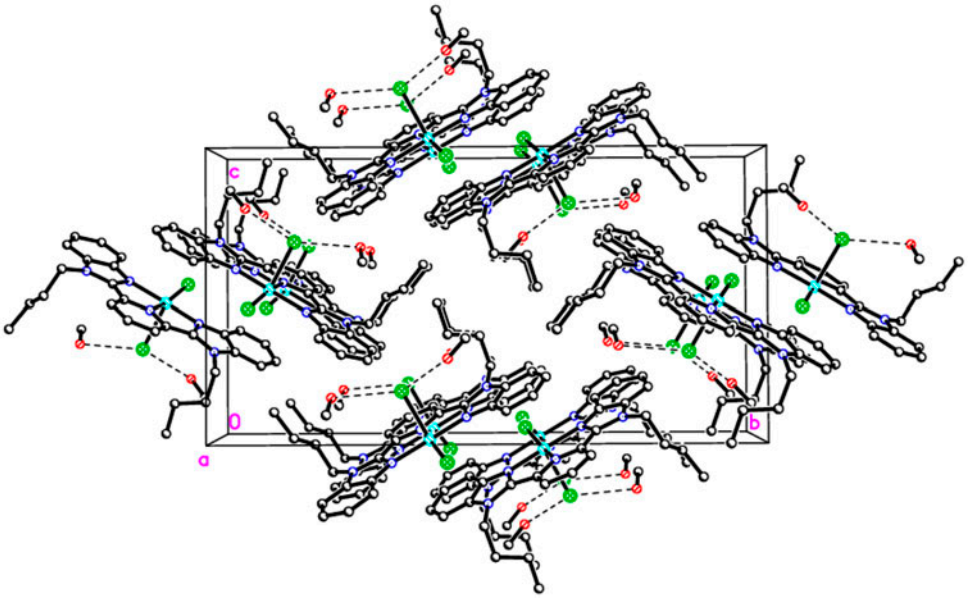


Figure 7. Packing plot of $[Cu(L)Cl_2]\cdot 2MeOH$. Hydrogens are removed for clarity. Hydrogen bonding is shown as dashed lines.

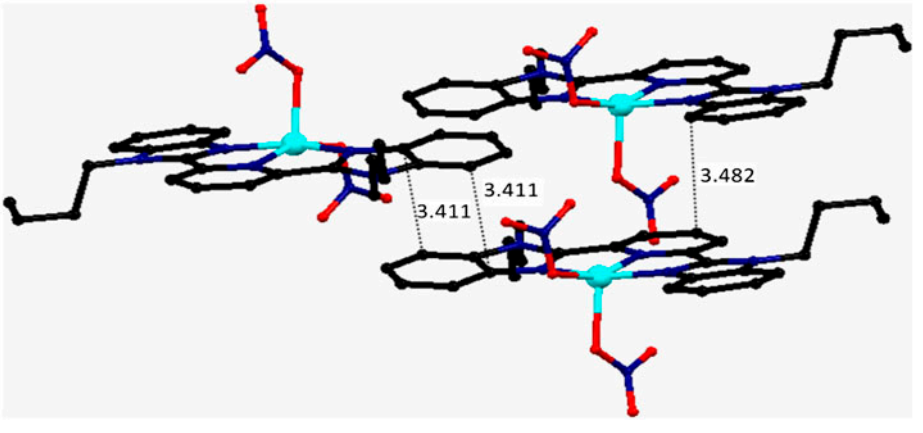


Figure 8. π–π interactions in the structure of $[Cu(L)(NO_3)_2]$; hydrogens are omitted for clarity.

is best described as a distorted square pyramid with three nitrogens of bzimpy and a water in the basal plane and a water at the axial position. Trigonality indexes (τ) are 0.205 and 0.1425 for $[Cu(bzimpy)Cl_2]\cdot DMF$ and $[Cu(bzimpy)(H_2O)_2](NO_3)_2$, respectively [31, 32].

3.2. *Antimicrobial activity studies*

The biological activities of the Cu(II) complexes were tested against bacteria and yeast. The organisms used in this study are *B. subtilis*, *B. cereus*, *E. coli*, *E. aerogenes*, *K. pneumoniaee*,

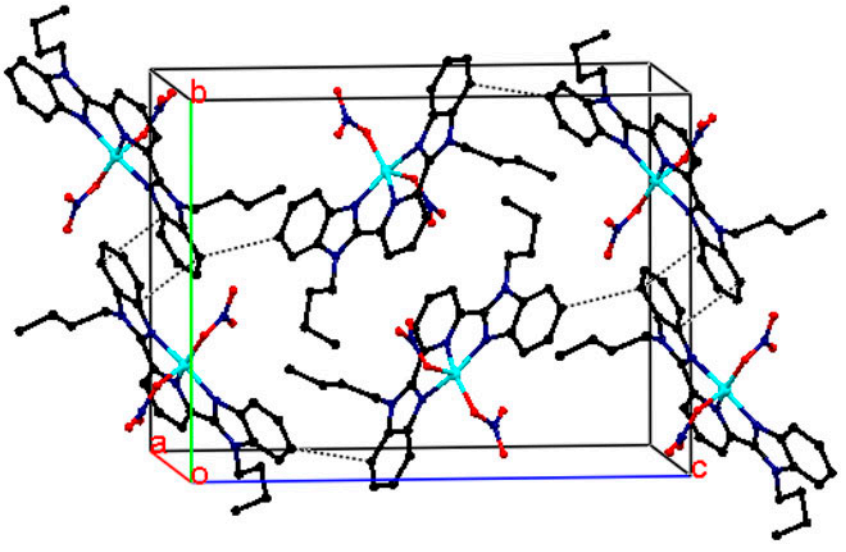


Figure 9. Packing plot of $[Cu(L)(NO_3)_2]$ showing interactions within the structure; hydrogens are removed for clarity.

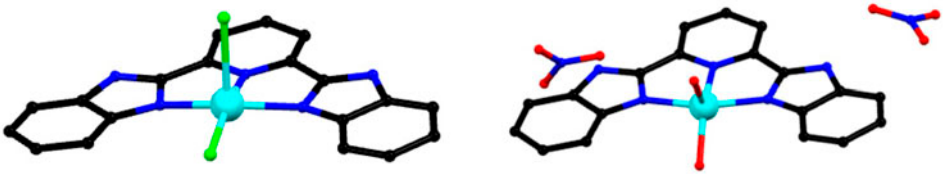


Figure 10. Molecular structures of $[Cu(bzimpy)Cl_2]\cdot DMF$ and $[Cu(bzimpy)(H_2O)_2](NO_3)_2$ redrawn from the literature [31, 32]. Hydrogens are omitted for clarity and a DMF solvate is not shown in the the structure of $[Cu(bzimpy)Cl_2]\cdot DMF$.

S. cerevisiae, *C. utilis*, and *C. albicans*. Disk diffusion agar technique was used to evaluate the antibacterial activity of the synthesized complexes. The results of the bactericidal screening of the synthesized compounds are given in table 5. The complexes $[Cu(L)(NO_3)_2]$ and $[Cu(L)Cl_2](CH_3OH)_2$ do not show antibacterial activity against *B. subtilis*, *B. cereus* and *E. aerogenes*, however, the complexes show antibacterial activity against *E. coli* and *K. pneumoniae*. The obtained data indicate that the complexes (700 µg) have weak antimicrobial activity compared to the standard antibiotic (Ampicillin 10 µg) against *E. coli* under identical experimental conditions. The complexes show antifungal activity against yeasts used in this study (*S. cerevisiae*, *C. utilis*, and *C. albicans*). The data show that the complexes have significant antifungal activity compared to Nystatin 100U (antifungal) against *S. cerevisiae*, *C. utilis*, and *C. albicans* under identical experimental conditions.

MIC of the complexes are similar and the complexes were active against some species at low concentration (table 6). However, antibacterial and antifungal activities of the complexes are much lesser than Ampicillin (standard antibiotic) and Nystatin (antifungal) (table 6). Complexes $[Cu(L)Cl_2](CH_3OH)_2$ and $[Cu(L)(NO_3)_2]$ were more effective against

Table 5. Antimicrobial activity data of the complexes (700 µg).

Compounds	*K. pneumoniae* Gram(−)	*E. aerogenes* Gram(−)	*E. coli* Gram(−)	*B. cereus* Gram(+)	*B. subtilis* Gram(+)	*S. cerevisiae* (Yeast)	*C. utilis* (Yeast)	*C. albicans* (Yeast)
[Cu(L)Cl1] $(CH_3OH)_2$	11 ± 2[a]	–	14 ± 0	–	–	28 ± 2	19 ± 2	20 ± 2
[Cu(L)$(NO_3)_2$]	13 ± 1	–	15 ± 2	–	–	25 ± 1	21 ± 0.00	17 ± 2
Ampicillin 10 µg (standard antibiotic)	17 ± 1	16 ± 1	11 ± 2	15 ± 2	12 ± 1	–	–	–
Nystatin 100U (antifungal)	–	–	–	–	–	17 ± 1	21 ± 2	19 ± 0
MeOH (control)	–	–	–	–	–	–	–	–

[a]Inhibition zone (mm); –: no inhibition zone.

S. cereviciae than the other micro-organisms with MIC values of 75 and 100 µg mL^{-1}, respectively, but do not show any activity against *B. subtilis*, *B. cereus,* and *E. aerogenes* at concentrations lower than 800 µg mL^{-1}. It is informative to compare antimicrobial activities of the complexes with two related Cu(II) complexes of 2-(2-pyridyl)benzimidazole (HPB), 2-(4′-thiazolyl)benzimidazole (TBZ) (table 6). The complex [Cu(HPB)(L-Arg)(H_2O)] $(ClO_4)_2$ derived from HPB and L-arginine was reported to exhibit higher antimicrobial activity on *E. coli* (MIC: 64 µg mL^{-1}) than the free ligand (HPB) and metal salt $Cu(ClO_4)_2$. The HPB and its Cu(II) complex [Cu(HPB)(L-Arg)(H_2O)]$(ClO_4)_2$ show lower MIC values than [Cu(L)Cl_2]$(CH_3OH)_2$ and [Cu(L)$(NO_3)_2$]; [Cu(L)Cl_2]$(CH_3OH)_2$ and [Cu(L)$(NO_3)_2$] are more effective on *E. coli* than $Cu(ClO_4)_2$. The complexes [Cu(TBZ)(Gly)(H_2O)]Cl and [Cu(HPB)(Gly)Cl]·$2H_2O$ derived from 2-(2-pyridyl)benzimidazole (HPB), 2-(4′-thiazolyl)

Table 6. MIC of the complexes (µg mL^{-1}).

Microorganisms	*K. pneumoniae*	*E. aerogenes*	*E. coli*	*B. subtilis*	*B. cereus*	*C. albicans*	*C. utilis*	*S. cerevisiae*	
[Cu(L)Cl_2] $(CH_3OH)_2$	300	>800	200	>800	>800	200	200	75	This work
[Cu(L)$(NO_3)_2$]	200	>800	200	>800	>800	200	200	100	This work
MeOH	>800	>800	>800	>800	>800	>800	>800	>800	This work
Ampicillin	3	3	4	4	4	–	–	–	This work
Nystatin/unite	–	–	–	–	–	40	30	30	This work
$Cu(ClO_4)_2$	–	–	256	320	–	–	–	–	[33]
HPB	–	–	160	256	–	–	–	–	[33]
[Cu(HPB)(L-Arg) (H_2O)]$(ClO_4)_2$	–	–	64	80	–	–	–	–	[33]
$CuCl_2$	–	–	–	256	–	–	–	–	[34]
TBZ	–	–	–	512	–	–	–	–	[34]
[Cu(TBZ)(Gly) (H_2O)]Cl	–	–	–	128	–	–	–	–	[34]
[Cu(HPB)(Gly)Cl] $2H_2O$	–	–	–	32	–	–	–	–	[34]

Note: HPB: 2-(2-pyridyl)benzimidazole; TBZ: 2-(4′-thiazolyl)benzimidazole; L-Arg: L-arginine; Gly: glycinate; –: not measured.

benzimidazole (TBZ), and glycinate (Gly) have been tested on *B. subtilis* (table 6). The complexes were more effective on *B. subtilis* than free ligands (HPB and TBZ) and metal salts ($Cu(ClO_4)_2$ and $CuCl_2$). The complexes prepared in this study are not effective on *B. subtilis*.

4. Conclusion

Two mononuclear copper(II) complexes of an N-alkylated benzimidazole (L) were synthesized and characterized by spectroscopic and analytic methods. Molecular structures of the complexes were determined by single-crystal X-ray diffraction study. The complexes $[Cu(L)(NO_3)_2]$ and $[Cu(L)Cl_2](CH_3OH)_2$ show considerable antimicrobial activity against *E. coli*, *K. pneumonia*, *S. cerevisiae*, *C. utilis* and *C. albicans*. The complexes do not show antibacterial activity against *B. subtilis*, *B. cereus*, and *E. aerogenes*.

Supplementary material

Crystallographic data have been deposited with the Cambridge Crystallographic Data Center; CSD references for $[Cu(L)Cl_2]\cdot 2MeOH$ and $[Cu(L)(NO_3)_2]$ are 984502 and 984503, respectively. Copies of this information can be obtained from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44 1223 335033; E-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

References

[1] L.E. Kapinos, B. Song, H. Sigel. *Inorg. Chim. Acta*, **280**, 50 (1998).
[2] C.J. Matthews, W. Clegg, S.L. Heath, N.C. Martin, M.N.S. Hull, J.C. Lockhart. *Inorg. Chem.*, **37**, 199 (1998).
[3] X.S. Tan, J. Sun, C.H. Hu, D.G. Fu, D.F. Xiang, P.J. Zheng, W.X. Tang. *Inorg. Chim. Acta*, **257**, 203 (1997).
[4] S. Emami, A. Foroumadi, M. Falahati, E. Lotfali, S. Rajabalian, S. Ahmed Ebrahimi, S. Farahyarc, A. Shafiee. *Bioorg. Med. Chem. Lett.*, **18**, 141 (2008).
[5] R.K. Ujjinamatada, A. Baier, P. Borowski, R.S. Hosmane. *Bioorg. Med. Chem. Lett.*, **17**, 2285 (2007).
[6] T.M. Kalyankar, S.S. Pekamwar, S.J. Wadher, P.S. Tiprale, G.H. Shinde. *Int. J. Chem. Pharm. Sci.*, **3**, 1 (2012).
[7] S. Gupta, M.K. Maheshwari. *Chem. Sci. Trans.*, **2**, 927 (2013).
[8] H.A. Barker, R.D. Smyth, H. Weissbach, J.I. Toohey, J.N. Ladd, E. Volcani. *J. Biol. Chem.*, **235**, 480 (1960).
[9] K.K. Mothilal, C. Karunakaran, A. Rajendran, R. Murugesan. *J. Inorg. Biochem.*, **98**, 322 (2004).
[10] V. Klimešová, J. Kočí, M. Pour, J. Stachel, K. Waisser, J. Kaustová. *Eur. J. Med. Chem.*, **37**, 409 (2002).
[11] E. Lukevics, P. Arsenyan, I. Shestakova, I. Domracheva, A. Nesterova, O. Pudova. *Eur. J. Med. Chem.*, **36**, 507 (2001).
[12] S. Özden, D. Atabey, S. Yildiz, H. Göker. *Bioorg. Med. Chem.*, **13**, 1587 (2005).
[13] Y. He, B. Wu, J. Yang, D. Robinson, L. Risen, R. Ranken, L. Blyn, S. Sheng, E.E. Swayze. *Bioorg. Med. Chem. Lett.*, **13**, 3253 (2003).
[14] X. Xu, Z. Xi, W. Chen, D. Wang. *J. Coord. Chem.*, **60**, 2297 (2007).
[15] G. Muller, J.C.G. Bunzli, K.J. Schenk, C. Piguet, G. Hopfgartner. *Inorg. Chem.*, **40**, 2642 (2001).
[16] A.Y.Y. Tam, W.H. Lam, K.M.C. Wong, N. Zhu, V.W.W. Yam. *Chem. Eur. J.*, **14**, 4562 (2008).
[17] M. Devereux, M. McCann, D.O. Shea, R. Kelly, D. Egan, C. Deegan, K. Kavanagh, V. McKee, G. Finn. *J. Inorg. Biochem.*, **98**, 1023 (2004).
[18] R. Boča, L. Dlháň, W. Linert, H. Ehrenberg, H. Fuess, W. Haase. *Chem. Phys. Lett.*, **307**, 359 (1999).
[19] R. Boc˘a, P. Baran, M. Boc˘a, L. Dlhán, H. Fuess, W. Haase, W. Linert, B. Papa´nkova´, R. Werner. *Inorg. Chim. Acta*, **278**, 190 (1998).
[20] B. Machura, A. Świtlicka, M. Penkala. *Polyhedron*, **45**, 221 (2012).
[21] W. Si-iuangxi, Z. Ying, Z. Fangjie, W. Qiuying, W. Liufang. *Polyhedron*, **2**, 1909 (1992).

[22] X.Q. Bai, S.H. Zhang. *Acta Cryst.*, **E65**, m397 (2009).
[23] M. Boča, R.F. Jameson, W. Linert. *Coord. Chem. Rev.*, **255**, 290 (2011).
[24] Bruker. *APEX2 and SAINT*, Bruker AXS Inc., Madison, WI (1998).
[25] G.M. Sheldrick. *Acta Cryst.*, **A64**, 112 (2008).
[26] A.W. Addison, P.J. Burke. *J. Heterocycl. Chem.*, **18**, 803 (1981).
[27] V. McKee, M. Zvagulis, J.V. Dagdigian, M.G. Patch, C.A. Reed. *J. Am. Chem. Soc.*, **106**, 4765 (1984).
[28] C.H. Collins, P.M. Lyne, J.M. Grange. *Microbiological Methods*, Butterworths & Co., Ltd, London (1989).
[29] L.J. Bradshaw. *Laboratory Microbiology*, 4th Edn, Saunders College Publishing, Ft. Worth, TX (1992).
[30] A.W. Addison, T.N. Rao, J. Reedijk, J. van Rijn, G.C. Verschoor. *J. Chem. Soc., Dalton Trans.*, 1349 (1984).
[31] G. Bernardinelli, G. Hopfgartner, A.F. Williams. *Acta Cryst.*, **C46**, 1642 (1990).
[32] S. Dey, S. Sarkar, H. Paul, E. Zangrando, P. Chattopadhyay. *Polyhedron*, **29**, 1583 (2010).
[33] Z.B. Ou, Y.H. Lu, Y.M. Lu, S. Chen, Y.H. Xiong, X.H. Zhou, Z.W. Mao, X.Y. Le. *J. Coord. Chem.*, **66**, 2152 (2013).
[34] J.Y. Chen, X.X. Ren, Z.W. Mao, X.Y. Le. *J. Coord. Chem.*, **65**, 2182 (2012).