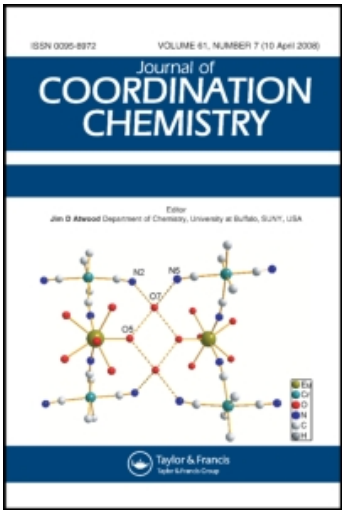

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Synthesis and antimicrobial activities of metal(II) complexes with *bis*(2,4-diiodo-6-propyliminomethyl-phenol)-pyridine

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Synthesis and antimicrobial activities of metal(II) complexes with *bis*(2,4-diiodo-6-propyliminomethyl-phenol)-pyridine

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Seven new mononuclear complexes have been synthesized from 2,4-diiodo-6-propyliminomethyl-phenol in pyridine and $Cu(OAc)_2 \cdot H_2O$, $Ni(OAc)_2 \cdot 4H_2O$, $Co(OAc)_2 \cdot 4H_2O$, $Zn(OAc)_2 \cdot 2H_2O$, $Cd(OAc)_2 \cdot 2H_2O$, $Mn(OAc)_2 \cdot 4H_2O$, and $Hg(OAc)_2$. The complexes were characterized by UV, IR, ESI-MS, and elemental analyses; *bis*(2,4-diiodo-6-propyliminomethyl-phenol)-pyridine-copper(II) (**1**) was characterized by X-ray crystallography. The central metal in each complex is five-coordinate by two nitrogens and two oxygens from two 3,5-diiodosalicylaldehyde Schiff-base ligands and one nitrogen from pyridine. The 3,5-diiodosalicylaldehyde Schiff base is bidentate. All the complexes were assayed for antibacterial (*Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Enterobacter cloacae*) activities by the MTT method. Complex **1** showed the most favorable antimicrobial activity with minimum inhibitory concentrations of 6.25, 3.125, 6.25, 3.125, 6.25, 3.125 $\mu g\,mL^{-1}$ against *B. subtilis*, *S. aureus*, *S. faecalis*, *P. aeruginosa*, *E. coli*, and *E. cloacae*, respectively.

Keywords: 3,5-Diiodosalicylaldehyde; *n*-Propylamine; Metal(II) complexes; Antibacterial activity

1. Introduction

Structure–activity relationships (SAR) of Schiff bases [1–4] have received attention with salicylaldehyde Schiff bases and their metal complexes showing antimicrobial properties [5–8]. Salicylaldehyde derivatives, with one or more haloatoms in the aromatic ring, show antibacterial and antifungal activities [9]. In this article, seven new mononuclear complexes condensed from 3,5-diiodosalicylaldehyde with *n*-propylamine and different metal ions have been synthesized. All the complexes were assayed for antibacterial activities against three Gram-positive bacterial strains (*Bacillus subtilis*, *Staphylococcus aureus*, and *Streptococcus faecalis*) and three Gram-negative bacterial strains (*Escherichia coli*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae*) by MTT (3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) method. Most complexes

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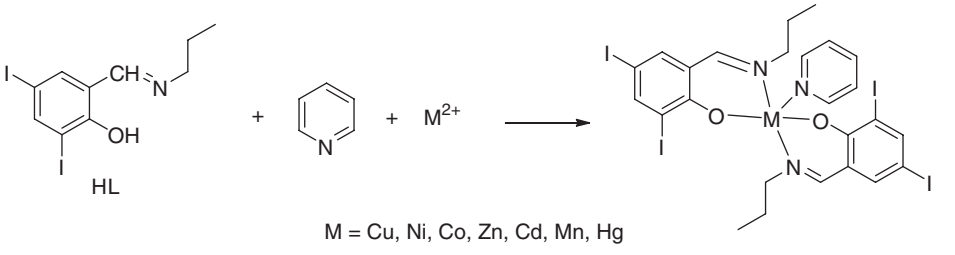
showed potent antibacterial activity against the six bacterial strains, adding to understanding of the antimicrobial activity of metal(II) complexes with 3,5-diiodosalicylalidene Schiff bases.

2. Experimental

2.1. *Chemistry*

The 2,4-diiodo-6-propyliminomethyl-phenol (HL) was synthesized with 3,5-diiodo-salicylaldehyde and *n*-propylamine. Reaction of the Schiff base with $Cu(OAc)_2 \cdot H_2O$, $Ni(OAc)_2 \cdot 4H_2O$, $Co(OAc)_2 \cdot 4H_2O$, $Zn(OAc)_2 \cdot 2H_2O$, $Cd(OAc)_2 \cdot 2H_2O$, $Mn(OAc)_2 \cdot 4H_2O$, and $Hg(OAc)_2$ in pyridine led to seven new mononuclear complexes (scheme 1). All complexes gave satisfactory chemical analyses (±0.4%). UV, IR, and ESI-MS spectra were consistent with the assigned structures. The crystal structure of **1** was determined using Enraf-Nonius CAD-4 four-circle single crystal X-ray diffractometer. Single crystals of **1** ($0.20 \times 0.05 \times 0.05\,mm^3$) were chosen for X-ray diffraction. The data were collected with graphite-monochromated Mo-Kα radiation ($\lambda = 071073$ Å) using ω–2θ scan technique. Complex **1** is an olive block crystal. A total of 5965 reflections were collected and 5312 were independent ($R_{int} = 0.0334$), of which 3661 observed reflections had $I > 2\sigma(I)$. The structure was solved using direct methods and refined by full-matrix least-squares. All nonhydrogen atoms were assigned anisotropic displacement parameters in the refinement. All hydrogens were added at calculated positions and refined using a riding model. The structures were refined on F^2 using SHELXTL-97 [10]. The crystal used for the diffraction study showed no decomposition during data collection. The crystal and refinement data are listed in table 1. Selected bond lengths and angles are given in table 2. The 3,5-diiodosalicylalidene was synthesized with salicylaldehyde, KI, and KIO_3 [11]. Chemicals (reagent grade) were commercially available. UV spectra were recorded on a U-3000 Spectrophotometer. IR spectra were recorded on a Nexus 870 FT-IR. ESI-MS spectra were recorded on a Mariner System 5304 Mass Spectrometer. Elemental analyses were performed on a CHN-O-Rapid instrument and were within 0.4% of the theoretical values. Melting points were measured on a Boetius micro melting point apparatus.

Equimolar quantities (0.4 mmol) of 3,5-diiodosalicylaldehyde and *n*-propylamine were dissolved in methanol (10 mL) and stirred at room temperature for 10 min to give a clear solution. After standing for approximately 3 days, precipitates were separated



Scheme 1. Syntheses of the complexes.

Table 1. Crystallographic and experimental data for **1**.

Empirical formula	$C_{25}H_{25}I_4N_3O_2Cu$
Formula weight	970.62
Crystal system	Monoclinic
Space group	$P2(1)/n$
Unit cell dimensions (Å, °)	
a	15.828(3)
b	9.938(2)
c	21.883(4)
α	90
β	104.03(3)
γ	90
Volume (Å^3), Z	3339.5(12), 4
Temperature (K)	293(2)
Density (g cm^{-3})	1.931
Absorption coefficient (mm^{-1})	4.375
$F(000)$	1812
Max. and min. transmission	0.8109 and 0.4749
Data/restraints/parameters	5965/49/292
θ range (°)	1.44–25.17
Index ranges (h, k, l)	$-18 \le h \le 18$; $0 \le k \le 11$; $0 \le l \le 26$
Reflections collected	5965
Independent reflection	5965 [R(int) = 0.0000]
$R(I > 2\sigma(I))$[a]	0.0680
$wR(I > 2\sigma(I))$[b]	0.1793
Largest difference peak and hole (e Å^{-3})	1.320 and −1.875

[a] $R = \sum ||F_o| - |F_c| / \sum |F_o||$, [b] $wR = \left[\left[\sum \left(F_o^2 - F_o^2\right)^2\right] / \sum \left[w\left(F_o^2\right)^2\right]\right]^{1/2}$.

Table 2. Selected bond lengths (Å) and angles (°) of **1**.

Cu–O(2)	1.927(8)	Cu–O(1)	1.955(7)	Cu–N(1)	2.098(1)
Cu–N(2)	2.108(1)	Cu–N(3)	2.144(1)	I(1)–C(13)	2.099(1)
O(1)–C(12)	1.245(1)	N(1)–C(18)	1.250(2)	N(1)–C(3)	1.455(2)
C(1)–C(2)	1.522(2)	I(2)–C(15)	2.125(1)	O(2)–C(19)	1.311(1)
C(2)–C(3)	1.61(2)	N(3)–C(7)	1.322(2)	N(3)–C(11)	1.332(2)
I(3)–C(22)	2.125(1)	N(2)–C(25)	1.251(1)	N(2)–C(6)	1.464(2)
I(4)–C(20)	1.108(1)				
O(2)–Cu–O(1)	177.5(3)	O(2)–Cu–N(1)	93.5(4)	O(1)–Cu–N(1)	88.1(4)
O(2)–Cu–N(2)	88.7(4)	O(1)–Cu–N(2)	92.3(4)	N(1)–Cu–N(2)	117.5(4)
O(2)–Cu–N(3)	88.6(4)	O(1)–Cu–N(3)	88.9(3)	N(1)–Cu–N(3)	120.8(4)
N(2)–Cu–N(3)	121.8(4)	C(12)–O(1)–Cu	125.6(7)	C(18)–N(1)–C(3)	115.8(1)
C(18)–N(1)–Cu	121.7(9)	C(3)–N(1)–Cu	121.9(9)	C(19)–O(2)–Cu	128.6(7)
C(7)–N(3)–C(11)	115.6(1)	C(7)–N(3)–Cu	122.3(9)	C(11)–N(3)–Cu	122.1(9)
N(1)–C(3)–C(2)	107.7(1)	C(25)–N(2)–C(6)	119.5(1)	C(25)–N(2)–Cu	119.8(8)
C(6)–N(2)–Cu	120.6(8)	N(2)–C(6)–C(5)	112.7(1)	N(3)–C(7)–C(8)	122.6(2)
N(3)–C(11)–C(10)	122.0(2)	O(1)–C(12)–C(13)	120.7(1)	O(1)–C(12)–C(17)	126.5(1)
C(14)–C(13)–I(1)	120.6(9)	C(12)–C(13)–I(1)	115.3(8)	C(14)–C(15)–I(2)	119.6(1)
C(16)–C(15)–I(2)	119.4(9)	N(1)–C(18)–C(17)	126.9(1)	O(2)–C(19)–C(20)	120.7(1)
O(2)–C(19)–C(24)	121.8(1)	C(19)–C(20)–I(4)	117.7(9)	C(21)–C(20)–I(4)	118.5(1)
C(21)–C(22)–I(3)	120.7(1)	C(23)–C(22)–I(3)	119.1(1)	N(25)–C(25)–C(24)	130.2(11)

by filtration, recrystallized from methanol, washed with methanol three times, and dried in a vacuum desiccator containing anhydrous $CaCl_2$ to give HL.

A 0.4 mmol HL with 0.2 mmol of metal acetate were dissolved in pyridine (5 mL) and stirred at room temperature for 15 min to give a clear solution. After standing for 10–15 days, precipitates were separated by filtration, washed with methanol three times, and dried in a vacuum desiccator containing anhydrous $CaCl_2$.

2.1.1. *Bis*(2,4-diiodo-6-propyliminomethyl-phenol)-pyridine-copper(II) (1). Olive-drab crystals, yield 80%, m.p.: 104–107°C. UV(λ nm): 259, 397. Selected IR data (cm^{-1}, KBr): 1624(s); 1601.4(s); 1449(s); 1211(s); 671(s). ESI-MS: 971.22 ($C_{25}H_{26}I_4N_3O_2Cu^+$, $[M+H]^+$). Anal. Calcd for $C_{25}H_{25}I_4N_3O_2Cu$: C, 30.94%; H, 2.60%; N, 4.33%. Found: C, 30.59%; H, 2.52%; N, 4.31%.

2.1.2. *Bis*(2,4-diiodo-6-propyliminomethyl-phenol)-pyridine-nickel(II) (2). Yellow green crystals, yield 76%, m.p.: 125–128°C. UV(λ nm): 260, 401. Selected IR data (cm^{-1}, KBr): 1626(s); 1597(s); 1455(s); 1213 (s); 669(s). ESI-MS: 966.36 ($C_{25}H_{26}I_4N_3O_2Ni^+$, $[M+H]^+$). Anal. Calcd for $C_{25}H_{25}I_4N_3O_2Ni$: C, 31.10%; H, 2.61%; N, 4.35%; Ni, 6.08%. Found: C, 31.03%; H, 2.57%; N, 4.32%; Ni, 6.13%.

2.1.3. *Bis*(2,4-diiodo-6-propyliminomethyl-phenol)-pyridine-cobalt(II) (3). Brown crystals, yield 74%, m.p.: 130–134°C. UV(λ nm): 263, 404. Selected IR data (cm^{-1}, KBr): 1621(s); 1597(s); 1444(s); 1211(s); 669(s). ESI-MS: 966.58 ($C_{25}H_{26}I_4N_3O_2Co^+$, $[M+H]^+$). Anal. Calcd for $C_{25}H_{25}I_4N_3O_2Co$: C, 31.10%; H, 2.61%; N, 4.35%; Co, 6.10%. Found: C, 31.05%; H, 2.62%; N, 4.38%; Co, 6.06%.

2.1.4. *Bis*(2,4-diiodo-6-propyliminomethyl-phenol)-pyridine-zinc(II) (4). Yellow crystals, yield 82%, m.p.: 123–126°C. UV(λ nm): 265, 388. Selected IR data (cm^{-1}, KBr): 1618(s); 1586(s); 1441(s); 1219(s); 670(s). ESI-MS: 973.04 ($C_{25}H_{26}I_4N_3O_2Zn^+$, $[M+H]^+$). Anal. Calcd for $C_{25}H_{25}I_4N_3O_2Zn$: C, 30.86%; H, 2.59%; N, 4.32%; Zn, 6.73%. Found: C, 30.75%; H, 2.52%; N, 4.28%; Zn, 6.64%.

2.1.5. *Bis*(2,4-diiodo-6-propyliminomethyl-phenol)-pyridine-manganese(II) (5). Brown crystals, yield 76%, m.p.: 220–224°C. UV(λ nm): 259, 399. Selected IR data (cm^{-1}, KBr): 1610(s); 1577(s); 1436(s); 1212(s); 671(s). ESI-MS: 962.61 ($C_{25}H_{26}I_4N_3O_2Mn^+$, $[M+H]^+$). Anal. Calcd for $C_{25}H_{25}I_4N_3O_2Mn$: C, 31.20%; H, 2.62%; N, 4.37%; Mn, 5.71%. Found: C, 31.15%; H, 2.67%; N, 4.29%; Mn, 5.68%.

2.1.6. *Bis*(2,4-diiodo-6-propyliminomethyl-phenol)-pyridine-cadmium(II) (6). Straw yellow crystals, yield 75%, m.p.: 133–137°C. UV(λ nm): 262, 390. Selected IR data (cm^{-1}, KBr): 1621(s); 1580(s); 1431(s); 1187(s); 671(s). ESI-MS: 1020.08 ($C_{25}H_{26}I_4N_3O_2Cd^+$, $[M+H]^+$). Anal. Calcd for $C_{25}H_{25}I_4N_3O_2Cd$: C, 29.41%; H, 2.47%; N, 4.12%; Cd, 11.02%. Found: C, 29.36%; H, 2.53%; N, 4.16%; Cd, 11.12%.

2.1.7. *Bis*(2,4-diiodo-6-propyliminomethyl-phenol)-pyridine-hydrargyrum(II) (7). Brilliant yellow crystals, yield 81%, m.p.: 180–183°C. UV(λ nm): 260, 432. Selected IR data (cm^{-1}, KBr): 1617(s); 1575(s); 1441(s); 1232(s); 671(s). ESI-MS: 1180.17 ($C_{25}H_{26}I_4N_3O_2Hg^+$, $[M+H]^+$). Anal. Calcd for $C_{25}H_{25}I_4N_3O_2Hg$: C, 25.42%; H, 2.14%; N, 3.56%; Hg, 17.00%. Found: C, 25.37%; H, 2.16%; N, 3.62%; Hg, 16.89%.

2.2. *Antimicrobial activity*

The antibacterial activities of the complexes were tested against *B. subtilis*, *S. aureus*, *S. faecalis*, *P. aeruginosa*, *E. coli*, and *E. cloacae* using MTT medium. The minimum inhibitory concentrations (MICs) of the test complexes were determined by a colorimetric method using the MTT dye [12]. A stock solution of the synthesized compound (50 μg mL^{-1}) in DMSO was prepared and quantities of the test complexes were incorporated in specified quantity of sterilized liquid medium. A specified quantity of the medium containing the complex was poured into microtitration plates. Suspension of the microorganism was prepared to contain approximately 10^5 cfu mL^{-1} and applied to microtitration plates with serially diluted complexes in DMSO to be tested, and incubated at 37°C for 24 h for bacteria. After the MICs were visually determined on each microtitration plates, 50 μL of phosphate buffered saline (PBS 0.01mol L^{-1}, pH 7.4: $Na_2HPO_4 \cdot 12H_2O$ 2.9 g, KH_2PO_4 0.2 g, NaCl 8.0 g, KCl 0.2 g, distilled water 1000 mL) containing 2 mg mL^{-1} of MTT was added to each well. Incubation was continued at room temperature for 4–5 h. The content of each well was removed, and 100 μL of isopropanol containing 5% 1 mol L^{-1} HCl was added to extract the dye. After 12 h of incubation at room temperature, the optical density (OD) was measured with a microplate reader at 570 nm. The observed MICs are presented in table 3.

3. Results and discussion

Complexes $C_{25}H_{25}I_4N_3O_2M$ (M = Cu, Ni, Co, Zn, Cd, Mn, or Hg) were prepared from 2,4-diiodo-6-propyliminomethyl-phenol ($C_{10}H_{11}I_2NO$) in pyridine, as described in the Experimental Section, in moderate yields (74–82%). The infrared spectra (KBr pellets) display an intense absorption at *ca* 1610–1625 cm^{-1} attributable to $\nu_{(C=N)imine}$. This band shifts *ca* 18–33 cm^{-1} to lower wavenumbers compared to the 1643 cm^{-1} of $C_{10}H_{11}I_2NO$. The UV spectra of the complexes display an intense absorption at 259–265 nm ($\pi \rightarrow \pi^*$) and 388–432 nm ($n \rightarrow \pi^*$).

The structure of *bis*(2,4-diiodo-6-propyliminomethyl-phenol)-pyridine-copper(II) was confirmed by single-crystal X-ray diffraction. The structure is a mononuclear complex (figure 1). The Cu(II) lies above the plane with pyridine occupying the axial position. The Cu–N(py) distance (Cu–N(3) 2.144(1) Å) is longer than the Cu–N (ligand) distance (Cu–N(1) 2.098(1) Å, Cu–N(2) 2.108(1) Å). The Cu–O(1) (1.955(7) Å) and Cu–O(2) (1.927(8) Å) bond lengths are in normal range. Figure 2 shows the packing structure of title complex along the *b*-axis.

The ways different metal(II) complexes react with bacteria vary due to the difference in the structures. Structural analysis of these complexes aids in structure–activity

Table 3. MICs of the synthetic complexes.

	Microorganisms MICs ($\mu g\,mL^{-1}$)					
	Gram positive			Gram negative		
Compounds	*B. subtilis*	*S. aureus*	*St. faecalis*	*P. aeruginosa*	*E. coli*	*E. cloacae*
1	6.25	3.125	6.25	3.125	6.25	3.125
2	3.125	6.25	25	6.25	12.5	12.5
3	25	25	25	6.25	12.5	25
4	12.5	12.5	25	6.25	12.5	25
5	25	6.25	3.125	3.125	25	50
6	3.125	6.25	6.25	12.5	25	25
7	12.5	6.25	12.5	6.25	6.25	12.5
HL	>50	>50	>50	25	50	50
Penicillin	1.562	1.562	1.562	6.25	6.25	3.125
Kanamycin	0.39	1.562	3.125	3.125	3.125	1.562

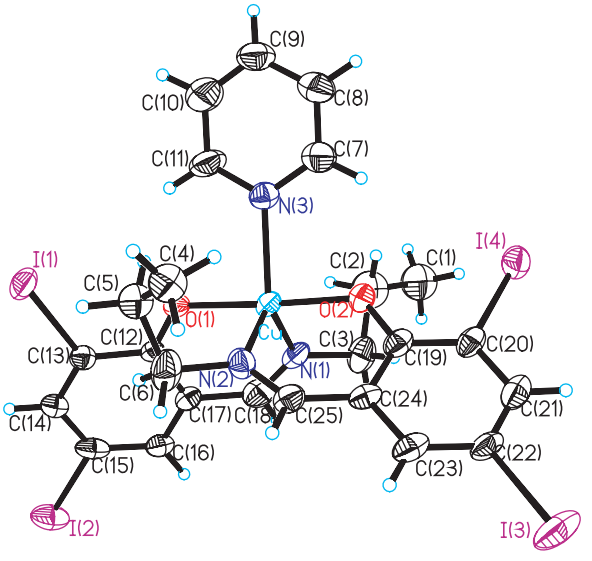


Figure 1. Crystal structure of **1** showing 30% probability displacement ellipsoids (arbitrary spheres for the H atoms).

relationships and may help in design of better inhibitors. Biological activity of a particular substance depends on a complex sum of properties including complex structure, affinity for the target site, and survival in the medium of application, survival within the biological system, transport properties, and state of the target organism [12]. In this study, we focus our attention on structure–activity relationships.

All the synthesized complexes and HL were screened for antibacterial activity against three Gram-positive bacterial strains (*B. subtilis*, *S. aureus*, and *St. faecalis*) and three Gram-negative bacterial strains (*E. coli*, *P. aeruginosa*, and *E. cloacae*) by the MTT method. The MICs of the complexes against six bacteria are presented in table 3. Also included was the activity of penicillin (North China Pharmaceutical Co. Ltd, D0211107, Hebei 050015, China) and kanamycin (Nanjing Zhuyan Biotechnology Co. Ltd,

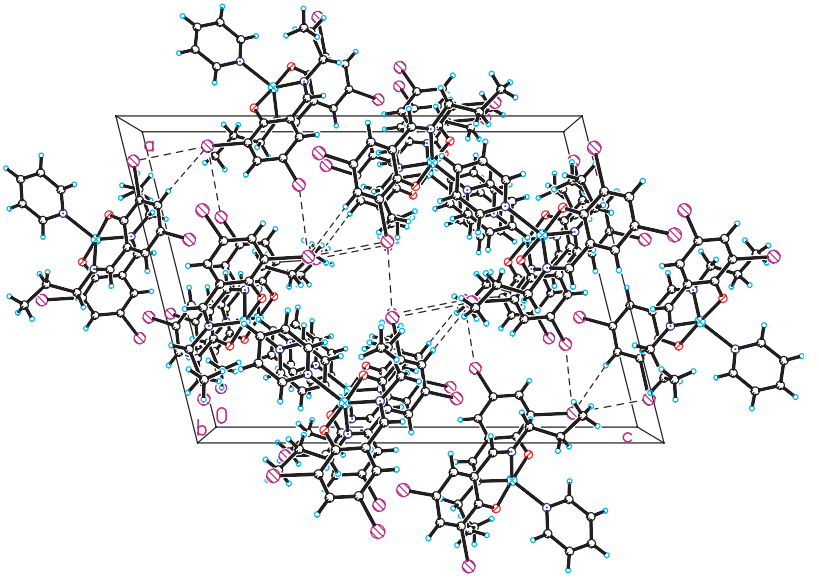


Figure 2. The packing structure of **1** along the *b*-axis.

Amresco 060D0504, Nanjing 210002, China) as reference compounds. The antibacterial activities of complexes were higher than HL. Complexes **1** and **7** showed significant activity against *E. coli* (MICs: 6.25 μg mL^{-1}) while **5** and **6** exhibited scarcely any activity (MICs > 25 μg mL^{-1}). Complex **1** exhibited significant activity against *E. cloacae* (MICs: 3.125 μg mL^{-1}) while **2** and **7** exhibited moderate activity (MICs: 12.5 μg mL^{-1}); the other complexes showed scarcely any activity (MICs > 25 μg mL^{-1}).

Complex **1** showed the most favorable antimicrobial activity with MICs (6.25, 3.125, 6.25, 3.125, 6.25, 3.125 μg mL^{-1}) against *B. subtilis*, *S. aureus*, *St. faecalis*, *P. aeruginosa*, *E. coli*, and *E. cloacae*, respectively. Complex **2** showed higher antimicrobial activity against *B. subtilis*, *S. aureus*, and *P. aeruginosa* (MICs < 6.25 μg mL^{-1}). Complex **3** showed moderate antimicrobial activity against *P. aeruginosa* and *E. coli* (MICs: 6.25–12.5 μg mL^{-1}). Complex **4** showed moderate antimicrobial activity against *B. subtilis*, *S. aureus*, *P. aeruginosa*, and *E. coli* (MICs 6.25–12.5 μg mL^{-1}). Complex **5** showed higher antimicrobial activity against *S. aureus*, *St. faecalis*, and *P. aeruginosa* (MICs < 6.25 μg mL^{-1}). Complex **6** showed higher antimicrobial activity against Gram-positive bacteria (*B. subtilis*, *S. aureus*, and *St. faecalis*) (MICs < 6.25 μg mL^{-1}). Complex **7** showed moderate antimicrobial activity with MICs (12.5, 6.25, 12.5, 6.25, 6.25, 12.5 μg mL^{-1}) against *B. subtilis*, *S. aureus*, *St. faecalis*, *P. aeruginosa*, *E. coli*, and *E. cloacae*, respectively.

Acknowledgements

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