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Synthesis, Structures, and Antibacterial Activities of Two Methanol Coordinated Zinc Complexes with Tetradentate Bis-Schiff Bases[1]

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Abstract—Two methanol coordinated zinc(II) complexes, [Zn(L^1)(MeOH)] (**I**) and [Zn(L^2)(MeOH)] (**II**), where L^1 and L^2 are the dianionic form of N,N'-*bis*(5-fluorosalicylidene)ethane-1,2-diamine and N,N'-*bis*(5-fluorosalicylidene)propane-1,2-diamine, respectively, have been synthesized and characterized by physical chemical methods and single crystal X-ray diffraction (CIF files CCDC nos. 950907 (**I**) and 950908 (**II**)). Crystallographic data for **I**: triclinic, $P\bar{1}$, a = 8.8765(8), b = 9.6577(9), c = 10.5117(9) Å, α = 114.590(2)°, β = 91.648(3)°, γ = 97.114(3)°, V = 809.87(13) Å^3, Z = 2, R_1 = 0.0307, wR_2 = 0.0698. Crystallographic data for **II**: orthorhombic, $Pca2_1$, a = 22.946(2), b = 7.6942(7), c = 9.6234(8) Å, V = 1699.0(2) Å^3, Z = 4, R_1 = 0.0320, wR_2 = 0.0676. X-ray crystal structural study indicated that the coordination environment around each zinc(II) atom in the complexes is a five-coordinated distorted pyramid in which the apical position is occupied by a methanol oxygen atom, and the basal plane is defined by the nitrogen and oxygen donor atoms of the Schiff base ligand. The antibacterial activities of the complexes were assayed.

Keywords: tetradentate Schiff base, crystal structure, zinc complexes, supramolecular self-assembly, antibacterial activity

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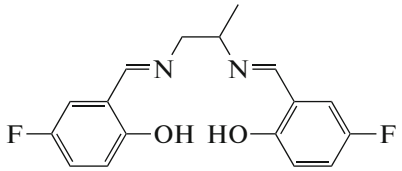
INTRODUCTION

Zinc is an important element for biological processes of human beings [1–3]. However, the mechanism of action of zinc in physiology and pathology are poorly understood. Zinc is also an essential cofactor in six classes of enzymes as well as in several families of regulatory proteins [4]. Its importance in DNA synthesis, control of gene expression, and induction of cell apoptosis is becoming better understood [5]. bis-Schiff bases derived from benzaldehydes with diamines are important ligands in the coordination of various metal atoms. Zinc complexes with Schiff bases have been received particular interest for their biological effects, especially antibacterial and antitumor activities [6–8]. Zinc is readily five- or six-coordinated, generating square pyramidal, trigonal bipyramidal, or octahedral geometry. For the bis-Schiff base zinc complexes with square pyramidal geometries, the basal planes are usually coordinated by the donor atoms of the Schiff base ligands, and the apical positions are occupied by anions such as nitrate, chloride, or neutralized ligands such as pyridine or water molecules [9–12]. However, methanol, as a widely used solvent for the preparation of such complexes, has seldom coordinated to zinc atoms. In addition, fluoro-substituted Schiff bases have been reported to possess potential antibacterial activities [13]. In the present work, two rarely seen methanol coordinated zinc(II) complexes, [Zn(L^1)(MeOH)] (**I**) and [Zn(L^2)-MeOH)] (**II**), derived from the fluoro-substituted bis-Schiff bases N,N'-bis(5-fluorosalicylidene)ethane-1,2-diamine (**H_2L^1**) and N,N'-bis(5-fluorosalicylidene)propane-1,2-diamine (**H_2L^2**), have been synthesized, characterized, and investigated for their antibacterial activities.



H_2L^1 (R = H), H_2L^2 (R = CH_3)

EXPERIMENTAL

Material and measurements. All chemical reagents and solvents were of analytical grade and were obtained from Sigma-Aldrich. Methanol was dried over molecular sieves (4 N) prior to use. Elemental

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analyses were performed on a Perkin-Elmer 2400 II elemental analyzer. Infrared spectra were recorded on a Perkin-Elmer RX I FT-IR spectrophotometer with KBr discs.

Synthesis of the Schiff bases H_2L^1 and H_2L^2 were carried out by refluxing hot ethanolic solution (30 mL) of 5-fluorosalicylaldehyde (0.02 mol) with ethane-1,2-diamine (0.01 mol) and propane-1,2-diamine (0.01 mol), respectively, for about 1 h. The precipitates formed during reflux were filtered, washed with cold EtOH, and recrystallized from hot $EtOH \cdot H_2L^1$. The yields of H_2L^1 and H_2L^2 were 87 and 92%, respectively.

For $C_{16}H_{14}N_2F_2O_2$ (H_2L^1)			
Anal. calcd., %:	C, 63.2;	H, 4.6;	N, 9.2.
Found, %:	C, 63.0;	H, 4.7;	N, 9.1.
For $C_{17}H_{16}N_2F_2O_2$ (H_2L^2)			
Anal. calc., %:	C, 64.1;	H, 5.1;	N, 8.8.
Found, %:	C, 64.3;	H, 5.0;	N, 8.7.

Synthesis of the complexes. A methanolic solution (10 mL) of Schiff base (0.1 mmol) was mixed with a methanolic solution (5 mL) of $ZnCl_2$ (0.1 mmol), and refluxed in a water bath for 1 h. The separated complex was filtered, washed thoroughly with water, methanol, ether, and finally dried in a vacuum over fused $CaCl_2$. The yields of **I** and **II** were 65 and 57%, respectively.

For $C_{17}H_{16}N_2F_2O_3Zn$ (**I**)			
Anal. calc., %:	C, 51.1;	H, 4.0;	N, 7.0.
Found, %:	C, 50.8;	H, 4.1;	N, 7.1.
For $C_{18}H_{18}N_2F_2O_3Zn$ (II)			
Anal. calc., %:	C, 52.3;	H, 4.4;	N, 6.8.
Found, %:	C, 52.1;	H, 4.3;	N, 6.6.

A small amount of these complexes was recrystallized from methanol, affording colorless single crystals suitable for X-ray analysis.

Single crystal X-ray diffraction. X-ray data for the complexes were collected on a Bruker SMART APEXII diffractometer equipped with graphite-monochromated MoK_α radiation (λ = 0.71073 Å). A preliminary orientation matrix and cell parameters were determined from three sets of ω scans at different starting angles. Data frames were obtained at scan intervals of 0.5° with an exposure time of 10 s frame^{-1}. The reflection data were corrected for Lorentz and polarization factors. Absorption corrections were carried out using SADABS. The structures were solved by direct methods and refined by full-matrix least-squares analysis using anisotropic thermal parameters for non-H atoms with the SHELXTL program [14]. The methanol H atoms were located from difference Fourier maps and refined isotropically, with O–H distances restrained to 0.85(1) Å. The remaining H atoms were calculated at idealized positions and refined with the riding models. Crystallographic data for the complexes are summarized in Table 1.

Supplementary material for structures has been deposited with the Cambridge Crystallographic Data Centre (CCDC nos. 950907 (I) and 950908 (II); deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Antibacterial activity test. The in vitro activity test was carried out using the growth inhibitory zone (well method) [15]. The potency of components was determined against the Gram-positive bacteria: *S. agalactiae* and *S. aureus* and the Gram-negative bacteria: *K. pneumoniae* and *P. aeruginosa*. Microorganisms were cultured on Muller–Hinton agar medium. The inhibitory activity was compared with that of standard antibiotics, such as gentamicine (10 μg). After drilling wells on medium using a 6-mm cork borer, 100 μL of solution from different compounds were poured into each well. The plates were incubated at 37°C overnight. The diameter of the inhibition zone was measured to the nearest. Each test was carried out in triplicate and the average was calculated for inhibition zone diameters. A blank containing only methanol showed no inhibition in a preliminary test. The macro-dilution broth susceptibility assay was used for the evaluation of minimal inhibitory concentration (**MIC**). By including 1 mL Muller-Hinton broth in each test, and then adding 1 mL extract with concentration 100 mg/mL in the first tube, we made serial dilution of this extract from first tube to last tube. Bacterial suspension prepared to match the turbidity of 0.5 Mcfarland turbidity standards. Matching this turbidity provides a bacterial inoculum concentration of 1.5×10^8 cfu/mL. Then 1 mL of bacterial suspension was added to each test tube. After incubation at 37°C for 24 h, the last tube was determined as the MIC without turbidity.

RESULTS AND DISCUSSION

Two rarely seen methanol coordinated zinc(II) complexes were synthesized by reaction of Schiff bases with zinc chloride in methanol. In fact, we have tried a lot of reaction systems for the preparation of these complexes, yet, the same products were obtained. The replacement of $ZnCl_2$ by $ZnBr_2$ or ZnI_2, as well as the addition of ammonium thiocyanate or sodium azide, can not interfere with the coordination of the methanol solvent.

The structures of both complexes are very similar to each other (Fig. 1). The Zn atom in each complex shows a distorted square pyramidal coordination geometry, with the two phenoxy oxygen atoms and two imino nitrogen atoms defining the basal coordination sites, while an O-coordinating methanol molecule occupies the apical position. The Zn atom deviates

Table 1. Crystallographic data and structure refinements for complexes **I** and **II**

Parameter	Value	
	I	**II**
Formula weight	399.69	413.71
Crystal size, mm	0.23 × 0.23 × 0.20	0.27 × 0.23 × 0.22
Temperature, °C	298(2)	298(2)
Crystal system	Triclinic	Orthorhombic
Space group	$P\bar{1}$	$Pca2_1$
a, Å	8.8765(8)	22.946(2)
b, Å	9.6577(9)	7.6942(7)
c, Å	10.5117(9)	9.6234(8)
α, deg	114.590(2)	90
β, deg	91.648(3)	90
γ, deg	97.114(3)	90
V, Å^3	809.87(13)	1699.0(2)
Z	2	4
ρ_{calcd}, g cm^{-3}	1.639	1.617
$\mu(MoK_\alpha)$, mm^{-1}	1.557	1.487
$F(000)$	408	848
Number of measured reflections	7947	12201
Unique reflections	2597	2697
Number of observations ($I > 2\sigma(I)$)	3010	3081
Independent parameters	230	240
Number of restraints	1	2
R_1, wR_2 ($I > 2\sigma(I)$)*	0.0307, 0.0698	0.0320, 0.0676
R_1, wR_2 (all data)*	0.0398, 0.0741	0.0408, 0.0707
Goodness of fit of F^2	1.054	1.034
Largest difference peak and hole, e Å^{-3}	0.272 and –0.222	0.424 and –0.359

* $R_1 = \Sigma\|F_o| - |F_c\|/\Sigma|F_o|$, $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$.

from the best coordination plane defined by the atoms N(1), N(2), O(1) and O(2) by 0.428(1) Å for **I** and 0.396(1) Å for **II** in direction of the apical methanol oxygen atom. The coordinate bond lengths and angles (Table 2) are comparable to each other, and also in line with the corresponding values found in related five-coordinated zinc(II) salen complexes [16, 17].

The question arises as to whether the coordination polyhedron around the five-coordinated zinc atoms can be described as a distorted square pyramid or a distorted trigonal bipyramid. Further information can be obtained by determining the structural index τ which represents the relative amount of trigonality (square pyramid, $\tau = 0$; trigonal bipyramid, $\tau = 1$); $\tau = (\beta - \alpha)/60°$, α and β being the two largest angles around the central atom [18]. The values of τ are 0.454 for **I** and 0.289 for **II**. Therefore, the coordination geometries of the zinc atoms in the complexes are best described as severely distorted square pyramids, instead of trigonal bipyramids.

In the crystal structure of **I**, two complex molecules are linked together by O–H···O hydrogen bonds (Table 3) to form a dimer (Fig. 2). In the crystal structure of **II**, the complex molecules are linked together by O–H···O hydrogen bonds (Table 3), to form 1D chains running along the z axis (Fig. 3).

The infrared spectra of the bis-Schiff bases and their complexes provide information about the metal-ligand bonding. The medium and broad absorptions in the 3200–3500 cm^{-1} region for the Schiff bases and the complexes substantiate the presence of O–H groups. Strong absorption at about 1655 cm^{-1} in the spectra of the bis-Schiff bases is assigned to the azomethine group, ν(C=N) [19]. The band undergoes negative shift of 12–19 cm^{-1} in the complexes, which can be attributed to donation of the nitrogen atom

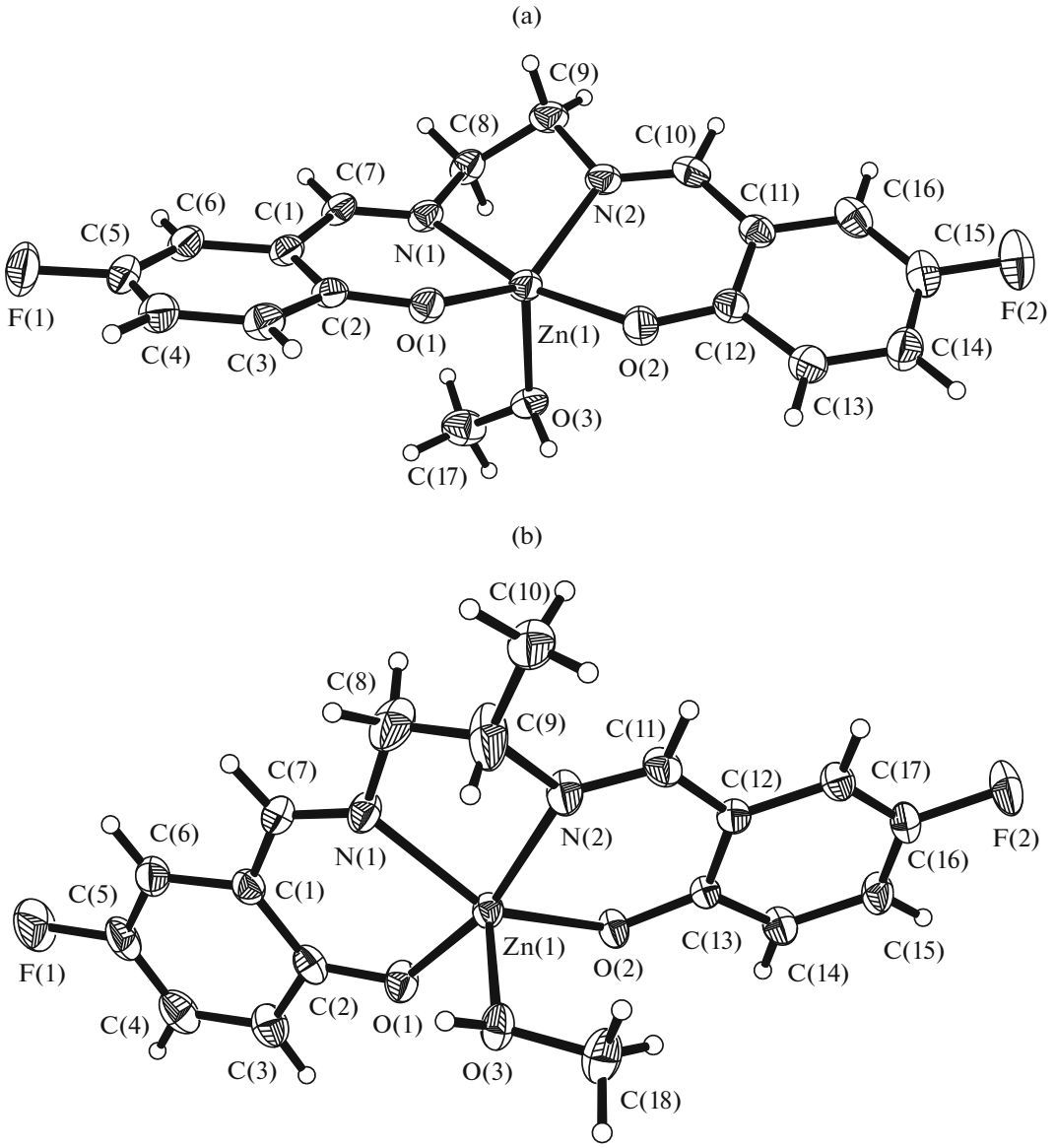

Fig. 1. ORTEP diagrams of complexes **I** (a) and **II** (b) with 30% thermal ellipsoids for all non-hydrogen atoms.

lone pair of the azomethine group to the metal ion. This conclusion is further supported by the presence of a medium band in the 510–590 cm^{-1} region for the complexes, which is absent in the spectra of the *bis*-Schiff bases. This band can be assigned to ν(Zn–N) [20]. The presence of a single band for ν(C=N) in the spectra of the complexes indicates participation of both the azomethine nitrogen atoms in coordination bond formation with the metal ion. The phenolic ν(C–O) in the free ligand exhibits a strong band at 1255 cm^{-1}. In the complexes, the band appears at about 1288 cm^{-1}. The weak bands in low wave numbers of about 430–480 cm^{-1} for the complexes may be assigned to ν(Zn–O) [20], and provides further evidence for coordination through the deprotonated phenolic oxygen atoms.

Antibacterial activities of the Schiff bases and the two complexes as well as the reference drug gentamicine are summarized in Table 4 (zone of growth inhibition) and Table 5 (minimal inhibitory concentrations). The results indicate strong activity of the free Schiff bases against Gram-positive bacteria, *S. agalactiae* and *S. aureus*, and moderate activities of them toward Gram-negative bacteria, *K. pneumoniae* and *P. aeruginosa*. The two Schiff base ligands were found to be equal activities against the bacteria, indicating the methyl substitute group is not in action. In comparison, the zinc complexes have stronger activities against all the bacteria than the free Schiff bases. The increased activity of the complexes may be explained on the basis of chelation theory; chelation reduces the polarity of the metal atom mainly because of partial

Table 2. Selected bond lengths (Å) and angles (deg) for **I** and **II**

Bond	*d*, Å	Bond	*d*, Å
I		**II**	
Zn(1)–O(1)	1.9918(15)	Zn(1)–O(1)	1.965(2)
Zn(1)–O(2)	1.9618(16)	Zn(1)–O(2)	1.992(2)
Zn(1)–O(3)	2.0773(17)	Zn(1)–O(3)	2.074(3)
Zn(1)–N(1)	2.0827(19)	Zn(1)–N(1)	2.073(3)
Zn(1)–N(2)	2.0921(19)	Zn(1)–N(2)	2.094(3)
Angle	ω, deg	Angle	ω, deg
O(2)Zn(1)O(1)	96.61(7)	O(1)Zn(1)O(2)	95.81(9)
O(2)Zn(1)O(3)	92.30(7)	O(1)Zn(1)N(1)	89.40(10)
O(1)Zn(1)O(3)	108.56(6)	O(2)Zn(1)N(1)	146.67(11)
O(2)Zn(1)N(1)	166.58(7)	O(1)Zn(1)O(3)	99.15(11)
O(1)Zn(1)N(1)	89.10(7)	O(2)Zn(1)O(3)	104.18(9)
O(3)Zn(1)N(1)	97.40(7)	N(1)Zn(1)O(3)	107.43(11)
O(2)Zn(1)N(2)	89.24(7)	O(1)Zn(1)N(2)	164.10(12)
O(1)Zn(1)N(2)	139.34(7)	O(2)Zn(1)N(2)	89.03(10)
O(3)Zn(1)N(2)	111.37(7)	N(1)Zn(1)N(2)	78.45(12)
N(1)Zn(1)N(2)	78.61(8)	O(3)Zn(1)N(2)	94.29(13)

Table 3. Geometric parameters of hydrogen bonds for **I** and **II***

D–H···A	Distance, Å			Angle D–H···A, deg
	D–H	H···A	D···A	
		I		
O(3)–H(3*A*)···O(1)^{i}	0.85(1)	1.82(1)	2.658(2)	174(3)
		II		
O(3)–H(3*A*)···O(2)^{ii}	0.85(1)	1.83(2)	2.671(3)	169(5)

* Symmetry codes: ^{i} $1-x$, $1-y$, $1/2+z$; ^{ii} $1-x$, $1-y$, $1-z$.

sharing of its positive charge with the donor groups and possible *p*-electron delocalization within the whole chelation. Also, chelation increases the lipophilic nature of the central atom which subsequently favors its permeation through the lipid layer of the cell membrane [21]. The quantitative assays gave MIC values in the range 3.125–50 mg mL^{-1}, that confirmed the above obtained results.

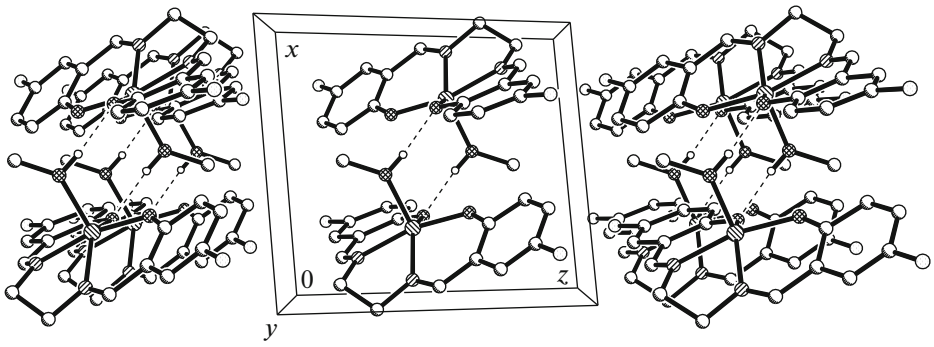

Fig. 2. Hydrogen bond (dashed lines) linked dimers of complex **I**, viewed along the *y* axis.

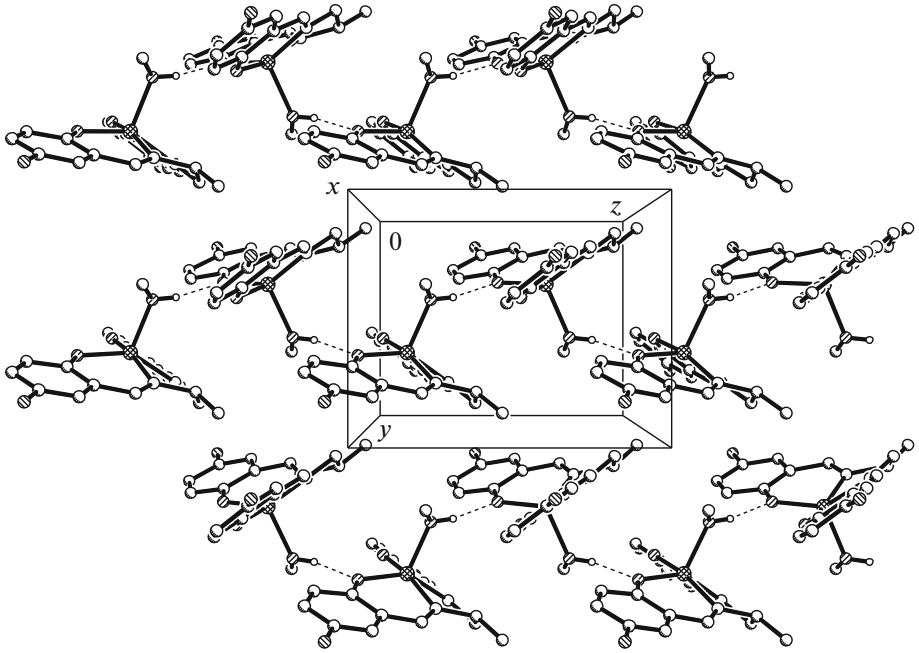

Fig. 3. Hydrogen bond (dashed lines) linked 1D chains of complex **II**, viewed along the *x* axis.

Thus, the present paper reports the synthesis, characterization and crystal structures of two rarely seen methanol coordinated zinc(II) complexes with fluoro-substituted bis-Schiff bases. The complexes show effective antibacterial activities against Gram-positive bacteria *S. agalactiae* and *S. aureus* and Gram-negative bacteria *K. pneumoniae* and *P. aeruginosa*. Further work might be carried out to explore more effective antibacterial materials based on the present complex models.

Table 4. Growth inhibition zone (mm) of the compounds

Bacterium	Compound				
	Gentamicine	H_2L^1	H_2L^2	**I**	**II**
S. agalactiae		30	30	50	50
S. aureus	20	40	30	50	50
K. pneumoniae	20	20	20	40	40
P. aeruginosa	15	20	20	30	30

Table 5. MIC (mg/mL) values of the compounds

Bacterium	Compound			
	H_2L^1	H_2L^2	**I**	**II**
S. agalactiae	12.5	12.5	6.25	6.25
S. aureus	12.5	12.5	3.125	3.125
K. pneumoniae	50	50	12.5	12.5
P. aeruginosa	25	25	12.5	12.5

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