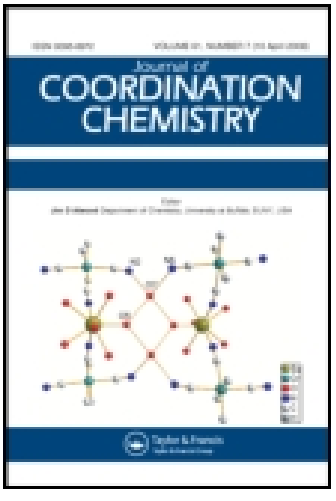

Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gcoo20

Synthesis, characterization, and antimicrobial activities of two mononuclear metal(II) complexes with (Z)-3-hydroxy-4-(3-hydroxy-3-phenylacryloyl)phenyl benzoate

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Published online: 14 Jul 2011.

To cite this article: Suo-Ping Xu, Ban-Feng Ruan, Qi-Yu Pan & Ren-Tao Hu (2011) Synthesis, characterization, and antimicrobial activities of two mononuclear metal(II) complexes with (Z)-3-hydroxy-4-(3-hydroxy-3-phenylacryloyl)phenyl benzoate, Journal of Coordination Chemistry, 64:14, 2489-2496, DOI: 10.1080/00958972.2011.601459

To link to this article: http://dx.doi.org/10.1080/00958972.2011.601459

Journal of Coordination Chemistry
Vol. 64, No. 14, 20 July 2011, 2489–2496

Synthesis, characterization, and antimicrobial activities of two mononuclear metal(II) complexes with (*Z*)-3-hydroxy-4-(3-hydroxy-3-phenylacryloyl)phenyl benzoate

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(*Received 26 January 2011; in final form 8 June 2011*)

Two mononuclear complexes with a β-diketone ligand (*Z*)-3-hydroxy-4-(3-hydroxy-3-phenylacryloyl)phenyl benzoate (**L**), $[CoL_2(CH_3CH_2OH)_2]$ (**1**), and $[MnL_2(CH_3CH_2OH)_2]$ (**2**) were prepared. Both complexes were characterized by X-ray crystallography, confirming that the central metal(II) are coordinated by four oxygens from two **L** and two oxygens from two ethanols. Both complexes were assayed for *in vitro* antibacterial (*Bacillus subtilis*, *Staphylococcus aureus*, *Streptococcus faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Enterobacter cloacae*) activities and showed better antimicrobial activity against Gram positive strains than Gram negative strains.

Keywords: β-Diketone ligand; Mononuclear complexes; Antibacterial activity

1. Introduction

β-Diketones are important intermediates in organic synthesis. The high reactivity of β-diketones such as 1,4-diphenyl-butane-1,3-dione, 1,4-dithiohene-butane-1,3-dione, 1,4-bis-(benzo(1,3)dio-butane-1,3-dione, 1,4-bis-(3-fluoro-4-methoxy-phenyl)-butane-1,3-dione, 3-hydroxy-1,3-diphenyl-propenone, and 1,3-di-furan-2-yl-3-hydroxy-propenone have been reported [1–4]. β-Diketones and their derivatives also have a wide range of applications in heat stabilizers, luminescence, catalysis, solvent extraction, and pharmaceuticals [5–11]. There were many methods for the preparation of β-diketones, but most of them could not provide satisfactory yields for a long time. Therefore, development of direct and efficient procedures for this class of compounds has been the target of synthetic organic chemistry. Recently, an operationally simple and new approach to synthesize β-diketones from zinc-mediated C–C bond sigmatropic rearrangement has been reported [12]. Herein, one bidentate β-diketone, (*Z*)-3-hydroxy-4-(3-hydroxy-3-phenylacryloyl)phenyl benzoate (**L**), was synthesized in good yield by microwave assistance and two mononuclear complexes were obtained by

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ISSN 0095-8972 print/ISSN 1029-0389 online © 2011 Taylor & Francis
DOI: 10.1080/00958972.2011.601459

reacting **L** with $CoCl_2 \cdot 6H_2O$ and $MnCl_2 \cdot 4H_2O$ in ethanol:acetone (1 : 1). Both 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 the 3-(4,5-dimethyl-2-triazyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) method.

2. Experimental

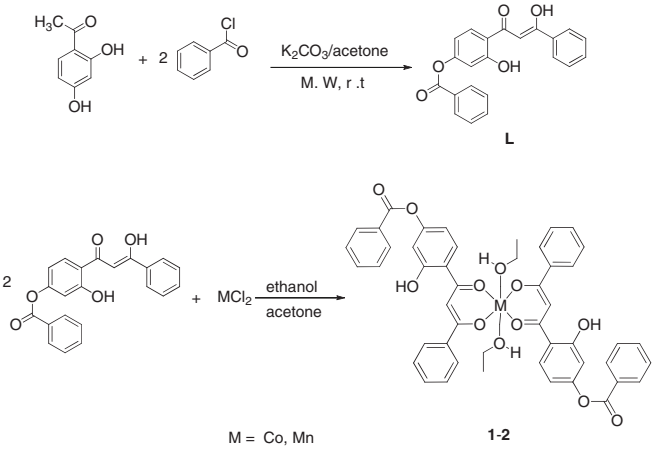
2.1. *Materials and instruments*

All chemicals were of reagent grade and used as received. 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.

2.2. *Preparation of L, 1, and 2*

Compound **L** was designed and synthesized from 2,4-dihydroxyacetophenone and benzoyl chloride in acetone by microwave assistance. The ligand was reacted with $CoCl_2 \cdot 6H_2O$ and $MnCl_2 \cdot 4H_2O$ in ethanol : acetone (1:1), respectively, and afforded bis(benzoic acid 3-hydroxy-4-(3-hydroxy-3-phenyl-acryloyl)-phenyl ester)-bis-ethanol-cobalt(II) **(1)** and bis(benzoic acid 3-hydroxy-4-(3-hydroxy-3-phenyl-acryloyl)-phenyl ester)-bis-ethanol-manganese(II) **(2)** (scheme 1).

2.2.1. Preparation of L. K_2CO_3 (20 g) was slowly added to a round-bottom-flask containing 2,4-dihydroxyacetophenone (3.04 g, 0.02 mol) and benzoyl chloride (5.6 g,



Scheme 1. Synthesis of **L**, **1**, and **2**.

0.04 mol) dissolved in acetone (50 mL). The mixture was microwave-irradiated (90 W) for 2 h and then precipitated. After filtration, the yellow solid was washed with acetone (100 mL) and water (200 mL), dried, and recrystallized from ethanol/acetone (1/1). Yield: 80%, m.p.: 241–243°C (lit. 240–243°C [13]). UV (λ nm): 377.5; 256.5. Selected IR data (cm^{-1}, KBr): 3421.5 (m), 1734.8 (s), 1599.3 (s), 1569.3 (s), 1508.1 (s), 1260.2 (s), 1205.3 (m), 1138.5 (s), 1062.8 (m), 1023.3 (m), 767.0 (m), 710.2 (s); ^{1}H-NMR ($CDCl_3$) δ ppm: 15.46 (s, 1H), 12.23 (s, 1H), 8.20 (d, $J = 7.1$ Hz, 2H), 7.95 (d, $J = 6.8$ Hz, 2H), 7.86 (d, $J = 8.8$ Hz, 1H), 7.66 (d, $J = 14.8$ Hz, 1H), 7.55 (d, $J = 12.6$ Hz, 4 H), 6.91 (d, $J = 2.4$, 1H), 6.85 (d, $J = 11.2$ Hz, 1H), 6.81 (s, 1H). ESI-MS: 361.10 ($C_{22}H_{17}O_5^+$, $[M+H]^+$). Anal. Calcd for $C_{22}H_{16}O_5$ (%): C, 73.33; H, 4.48. Found (%): C, 73.52; H, 4.45.

2.2.2. Compound 1. Compound **L** (0.360 g, 1 mmol) was added to an ethanol/acetone (1/1) solution (5 mL) of $CoCl_2 \cdot 6H_2O$ (0.237 g, 1 mmol) and stirred at room temperature for 15 min to give a clear solution. After standing for 10–15 days, the precipitates were separated by filtration, washed with ethanol thrice, and dried. Single crystals of **1** were obtained by slowly evaporating the methanol/ethyl ether solution. Yield: 75%, m.p.: 250–252°C. UV (λ nm): 373.0; 255.5. IR (cm^{-1}, KBr): 3400.5 (m), 3125.2 (m), 1735.4 (s), 1595.9 (s), 1558.7 (s), 1507.8 (s), 1483.2 (s), 1433.5 (s), 1292.6 (m), 1240.4 (s), 1205.3 (s); 1138.8 (s), 1062.0 (s), 1023.5 (m), 768.6 (m), 706.0 (s). Anal. Calcd for $C_{48}H_{42}O_{12}Co$ (%): C, 66.28; H, 4.87. Found (%): C, 66.32; H, 4.84.

2.2.3. Compound 2. Prepared accordingly using **L** and $MnCl_2 \cdot 4H_2O$. Yield: 81%, m.p.: 227–229°C. UV (λ nm): 377.5; 255.0. IR (cm^{-1}, KBr): 3385.3 (m), 3138.2 (m), 1733.6 (s), 1595.6 (s), 1559.9 (s), 1507.1 (s), 1483.4 (s), 1430.9 (m), 1290.8 (s), 1252.7 (s), 1205.3 (s); 1139.6 (s), 1062.3 (s), 1023.0 (m), 769.2 (m), 705.6 (s). Anal. Calcd for $C_{48}H_{42}O_{12}Mn$ (%): C, 65.59; H, 4.89. Found (%): C, 65.43; H, 4.82.

2.3. *Crystal structure determinations and refinements*

The crystallographic data for **1** and **2** were collected on a Bruker Smart 1000 CCD area detector diffractometer equipped with Mo-Kα ($\lambda = 0.71073$ Å) radiation using ω-scan mode. Empirical absorption correction was applied to the data. Unit cell dimensions were obtained with least-squares refinements, and all structures were solved by direct methods with SHELXL-97. All non-hydrogen atoms were located from the trial structure and then refined anisotropically. All hydrogens were generated in idealized positions. All calculations were performed with SHELXL-97 programs [14]. Other relevant parameters of the crystal structure are listed in table 1.

2.4. *Antimicrobial activity*

The antibacterial activity of **1** and **2** was tested against *B. subtilis*, *S. aureus*, *S. faecalis*, *P. aeruginosa*, *E. coli*, and *E. cloacae* using MTT medium. The MICs of the test complexes were determined by a colorimetric method using the dye MTT [15]. A stock solution of the synthesized complex (50 μg mL^{-1}) in DMSO was prepared and graded quantities of the test complexes were incorporated in a specified quantity of sterilized

Table 1. Crystallographic and experimental data for **1** and **2**.

	1	**2**
Empirical formula	$C_{48}H_{42}O_{12}Co$	$C_{48}H_{42}O_{12}Mn$
Crystal system	Triclinic	Triclinic
Formula weight	869.75	865.76
Space group	$P\bar{1}$	$P\bar{1}$
Unit cell dimensions (Å, °)		
a	7.2070(10)	7.1380(10)
b	9.4301(13)	9.377(4)
c	16.5509(18)	16.578(2)
α	106.360(2)	74.1510(10)
β	95.4320(10)	84.2010(10)
γ	90.9180(10)	89.363(2)
Volume (Å^3), Z	1073.4(2), 1	1061.8(5), 1
Calculated density (g cm^{-3})	1.346	1.354
Absorption coefficient (mm^{-1})	0.464	0.376
$F(000)$	453	451
Data/restraints/parameters	3728/0/296	3698/0/287
θ range for data collection (°)	2.25–25.02	2.26–25.021
R_{int}	0.0393	0.0293
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0646$, $wR_2 = 0.1203$	$R_1 = 0.0579$, $wR_2 = 0.1329$
Largest difference peak and hole (e Å^{-3})	0.326 and −0.396	0.275 and −0.226
Reflections collected/unique	5624/3728	5599/3698

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

Table 2. MICs of the compounds.

	MICs (μg mL^{-1})					
	Gram positive			Gram negative		
Compound	*B. subtilis*	*S. aureus*	*S. faecalis*	*S. faecalis*	*E. coli*	*E. cloacae*
1	6.25	12.5	6.25	12.5	12.5	6.25
2	12.5	6.25	6.25	12.5	12.5	12.5
L	25	12.5	12.5	25	25	25
PenicillinG	1.562	1.562	1.562	6.25	6.25	3.125
KanamycinB	0.39	1.562	3.125	3.125	3.125	1.562

liquid medium (MH medium for antibacterial activity). 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. After the minimum inhibitory concentrations (MICs) were visually determined on each of the microtitration plates, 50 μL of PBS (Phosphate Buffered Saline 0.01 mol 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 2.

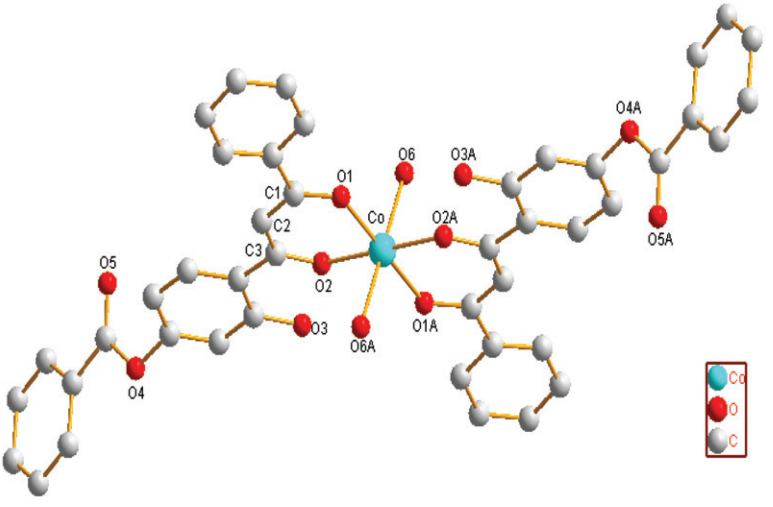


Figure 1. Molecular structure of **1** (all hydrogens and carbons of EtOH have been omitted for clarity).

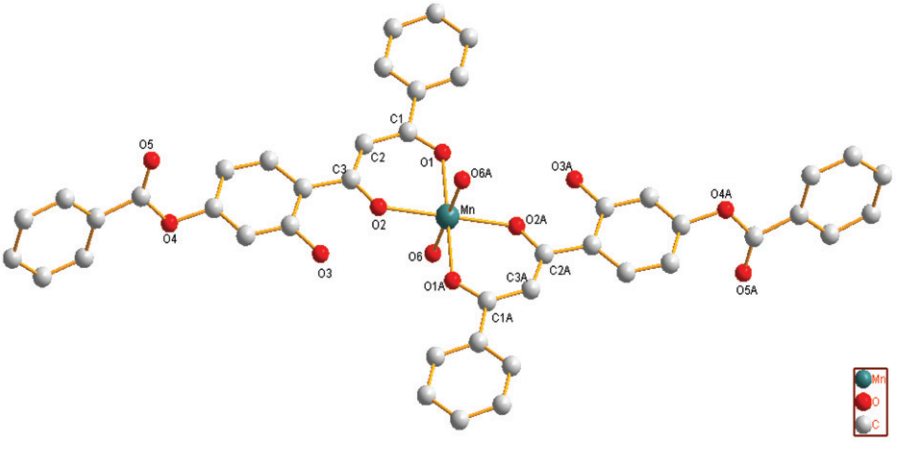


Figure 2. Molecular structure of **2** (all hydrogens and carbons of EtOH have been omitted for clarity).

3. Results and discussion

Complexes of formula $[L_2M(CH_3CH_2OH)_2]$ (M=Co and Mn) were prepared as described in section 2, in moderate yields (75–85%). IR spectra of all three complexes show four bands at 1480–1600 cm^{-1}, characteristic of the mixed modes of vibrations arising from normal coordinates having contributions from $\nu_{(C=O)}$ and $\nu_{(C=C)}$ of β-diketone groups [16]. The UV spectra of the complexes display intense absorptions at 255.0–258.5 nm ($\pi \rightarrow \pi^*$) and 368.0–377.5 nm ($n \rightarrow \pi^*$).

The structures of **1** and **2** were confirmed by single-crystal X-ray diffraction and are shown in figures 1 and 2, respectively; bond distances and angles are provided in table 3. Both complexes are electronically neutral mononuclear compounds. The central metals (Co and Mn), on an inversion center, are in pseudo octahedral coordination geometry

Table 3. Selected bond lengths (Å) and angles (°) of **1** and **2**.

1			
Co–O1	2.014(3)	Co–O2	2.033(2)
Co–O1A	2.014(3)	Co–O2A	2.033(2)
Co–O6	2.184(3)	Co–O6A	2.184(3)
O1–Co–O2	88.3(1)	O1–Co–O6A	85.5(1)
O1–Co–O2A	91.7(1)	O1–Co–O1A	180.0(0)
O1–Co–O6	94.5(1)		
2			
Mn–O1	2.084(2)	Mn–O2	2.118(2)
Mn–O1A	2.084(2)	Mn–O2A	2.118(2)
Mn–O6	2.245(3)	Mn–O6A	2.245(3)
O1–Mn–O2	84.4(9)	O1–Mn–O6	85.1(9)
O1–Mn–O6A	94.8(9)		

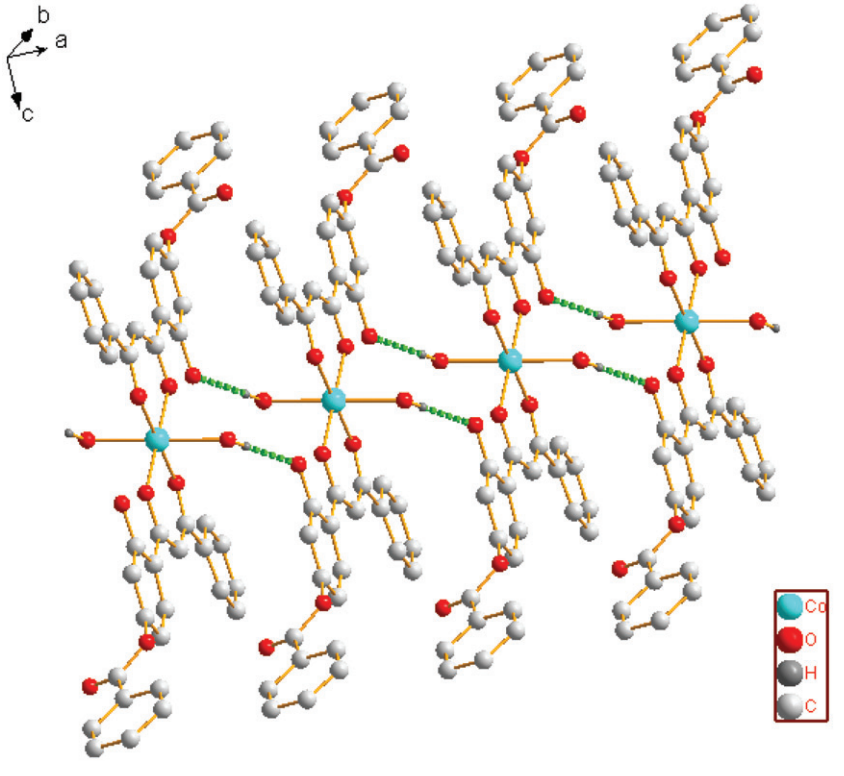


Figure 3. 1-D chains of **1** formed by intermolecular H bonds (O–H · · · O).

with two ethanols occupying both axial positions and oxygen donors from two β-diketone fragments binding in equatorial positions; each bis-β-diketonate is essentially planar [17]. The general M–O (M = Co, Mn) bond lengths are in the range 2.014(3)–2.245(3) Å, unexceptional and similar to the corresponding bonds in other cobalt and manganese diketonate complexes [18–20]. As shown in figures 3 and 4,

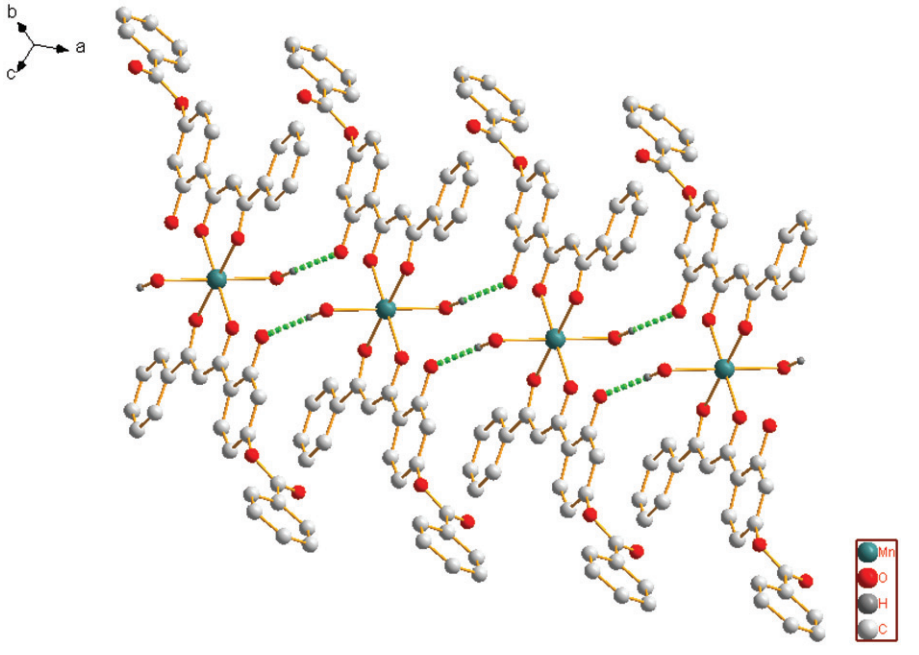


Figure 4. 1-D chains of **2** formed by intermolecular H bonds (O–H · · · O).

intermolecular H-bonds (O–H · · · O) formed between adjacent molecules lead to 1D chain structures for **1** and **2**, respectively. The H · · · O distances are 2.018(3) and 1.967(2) Å and the OH · · · O angles are 167.9(2)° and 163.7(2)° for **1** and **2**, respectively.

From MIC values (table 2), the complexes were more toxic towards Gram positive strains than Gram negative strains when compared to the positive controls penicillin and kanamycin, respectively. The reason may be the difference in the structures of the cell walls [21]. The walls of the Gram negative cells are more complex than those of Gram positive cells. Lipopolysaccharides form an outer lipid membrane and contribute to the complex antigenic specificity of Gram negative cells. Anti-microbial activity of complexes is due to either killing the microbes or inhibiting their multiplication by blocking their active sites [22]. Since the molecular structures are quite similar, the antibacterial activities of **1** and **2** are quite similar.

Acknowledgments

The work was co-financed by grants (Projects 30772627) from the National Natural Science Foundation of China and (Projects 09KJD150005) from Province Natural Science Foundation of Jiangsu, China.

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