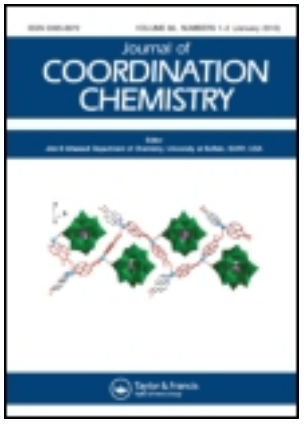

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Synthesis, crystal structure, and biological activities of a Zn(II) complex with a Se substituted Schiff base

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Synthesis, crystal structure, and biological activities of a Zn(II) complex with a Se substituted Schiff base

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A Zn(II) complex with an organoselenium substituted Schiff base, bis{2-[(benzylimino)methyl]-4,6-dihydroselenophenol}Zn(II), has been synthesized and characterized by elemental analyses and X-ray diffraction. Zn(II) is four-coordinated by two phenolate O and two imine N from two organoselenium substituted Schiff-base ligands, forming a distorted tetrahedral geometry. The title complex and its ligand were tested *in vitro* for their antibacterial and antitumor activity with the complex showing higher antibacterial and antitumor activities.

Keywords: Organoselenium; Schiff base; Zn complex; Crystal structure; Antibacterial; Antitumor

1. Introduction

Schiff bases and their metal complexes have received attention due to their various biological activities, antitumor [1–3], antimicrobial [3–5], and anti-inflammatory [6, 7]. Among these complexes, zinc complexes are particularly interesting. Zn complexes of substituted salicylaldimines have been reported to possess excellent photophysical properties for fluorescence sensing, such as nanosecond lifetimes and high quantum yields, and also undergo efficient energy transfer [8–10]. Zn complexes have also shown to be active as antitumor, antimicrobial, and antiglaucoma agents [11–15]. Selenium (Se) is a dietary essential trace element with important biological roles. Accumulating evidence indicates that Se compounds possess anticancer and antioxidant properties [16, 17]. Recently, it has also been reported that metal complexes of organoselenium substituted Schiff-base ligands exhibited antitumor activities by interaction with DNA [18, 19]. We were encouraged to synthesize a Zn(II) complex from an organoselenium substituted Schiff base condensed by 3,5-dihydroseleno-2-hydroxybenzaldehyde and phenylmethanamine. The antibacterial activities against *Bacillus subtilis* (gram-positive), *Staphylococcus aureus* (gram-positive), *Escherichia coli* (gram-negative), and *Pseudomonas fluorescence* (gram-negative), and their cytotoxic activities against three tumor cell lines, KB, K562, and Hep-G2 were evaluated.

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2. Experimental

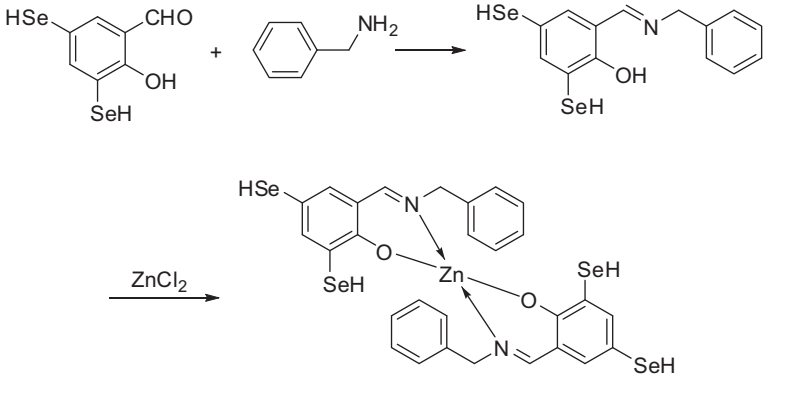
2.1. *Chemistry*

The organoselenium substituted Schiff base *(E)-2-((benzylimino)methyl)-4,6-dihydroselenophenol* was condensed by reacting with 3,5-dihydroseleno-2-hydroxybenzaldehyde and phenylmethanamine. Reaction of the Schiff base with $ZnCl_2$ in methanol led to a new mononuclear Zn(II) complex (scheme 1).

All chemicals were of reagent grade and used as received without purification. ^{1}H NMR spectra were recorded on a Bruker DPX 300 model spectrometer in DMSO-d_6. Chemical shifts (δ) for ^{1}H NMR spectra are reported in parts per million to residual solvent protons. ESI-MS spectra were recorded on a Mariner System 5304 Mass spectrometer. Elemental analyses were performed on a CHN–O–Rapid instrument.

2.1.1. Preparation of the Schiff base ligand. 564 mg (2 mmol) 3,5-dihydroseleno-2-hydroxybenzaldehyde and 214 mg (2 mmol) phenylmethanamine were dissolved in 10 mL methanol and stirred at room temperature for 30 min to give a clear solution. After standing for approximately 2 d, precipitates were separated by filtration, washed with methanol, and recrystallized from methanol to give *(E)-2-((benzylimino)methyl)-4,6-dihydroselenophenol*. Yield: 76%. ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 4.76 (s, 2H); 7.28–7.56 (m, 7H); 8.74 (s, 1H); 12.56 (s, 1H). ESI-MS: 371.9 ($C_{14}H_{14}NOSe_2^+$, $[M+H]^+$). Anal. Calcd for $C_{14}H_{13}NOSe_2$: C, 45.55%; H, 3.55%; N, 3.79%. Found: C, 45.64%; H, 3.50%; N, 3.83%.

2.1.2. Preparation of the Zn(II) complex. To a MeOH (10 mL) solution of $ZnCl_2$ (13.6 mg, 0.1 mmol), was added a MeOH solution (10 mL) of *(E)-2-((benzylimino)methyl)-4,6-dihydroselenophenol* (37.1 mg, 0.1 mmol). The mixture was stirred for 1 h at room temperature and then filtered. Upon keeping the filtrate in air for 7 days, colorless block-shaped crystals of Zn(II) complex, suitable for X-ray crystal determination, formed at the bottom of the vessel on slow evaporation of the solvent. The crystals were isolated, washed three times with MeOH, and dried in a vacuum desiccator containing anhydrous $CaCl_2$. Yield: 73%. Anal. Calcd for $C_{28}H_{24}N_2O_2Se_4Zn$: C, 41.95%; H, 3.02%; N 3.49%. Found: C, 42.10%; H, 3.06%; N 3.45%.



Scheme 1. Synthesis of Schiff base and complex.

2.2. *Crystal structure determination and refinement*

Crystallographic data for the Zn(II) complex are listed in table 1. The diffraction data were collected on a Nonius CAD4 diffractometer equipped with graphite-monochromated MoKα radiation (λ = 0.71073 Å). The structure was solved by direct methods and refined on F^2 by full-matrix least-squares using SHELX-97 [20]. All non-hydrogen atoms were refined anisotropically. All hydrogens were placed in calculated positions and assigned fixed isotropic thermal parameters at 1.2 times the equivalent isotropic U of the atoms to which they are attached and allowed to ride on their respective parent. The contributions of these hydrogens were included in the structure factors calculations. Selected bond lengths and angles are listed in table 2. Crystallographic data for this Zn(II) complex have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC 909211. Copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif by emailing data_request@ccdc.cam.ac.uk or by contacting The

Table 1. Crystallographic and experimental data for the complex.

Complex	Zn(II) complex
Formula	$C_{28}H_{24}N_2O_2Se_4Zn$
Formula weight	801.70
Crystal shape/color	Block/colorless
Crystal size (mm^3)	$0.24 \times 0.16 \times 0.16$
Crystal system	Monoclinic
Space group	*C2/c*
a (Å)	23.6698(5)
b (Å)	4.8418(2)
c (Å)	24.1968(5)
α (°)	90
β (°)	105.718(2)
γ (°)	90
Volume ($Å^3$)	2669.37(14)
Z	4
Dc/(g/cm^3)	1.955
μ (mm^{-1})	6.405
F (000)	1552
T/K	298(2)
θ range/°	2.82/28.32
Index ranges	$-31 \leqslant h \leqslant 31$ $-6 \leqslant k \leqslant 6$ $-32 \leqslant l \leqslant 27$
Reflections collected/unique	11,572/3289 [*R*(int) = 0.1044]
Data/restraints/parameters	3289/0/168
Max. and min. transmission	0.4272 and 0.3086
Goodness-of-fit on F^2	0.972
R_1, wR_2 [$I \geqslant 2\sigma(I)$][a]	0.0391, 0.1001
R_1, wR_2 (all data)[a]	0.0481, 0.1035
Largest diff. peak and hole ($eÅ^{-3}$)	0.993 and −0.648

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

Table 2. Selected bond lengths (Å) and angles (°) of the Zn(II) complex.

Zn(1)–O(1)	1.932(2)	Zn(1)–N(1)	2.010(3)
O(1)–Zn(1)–N(1)	94.59(9)	O(1)–Zn(1)–N(1)#1	113.84(10)
O(1)#1–Zn(1)–O(1)	125.11(14)	N(1)#1–Zn(1)–N(1)	116.64(15)

Symmetry transformations used to generate equivalent atoms: #1 −x + 2, y, −z + 1/2.

Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033.

2.3. *Antibacterial activity*

The antibacterial activities were tested against *B. subtilis*, *E. coli*, *P. fluorescence*, and *S. aureus* using MH medium (Mueller-Hinton medium: casein hydrolysate 17.5 g, soluble starch 1.5 g, and beef extract 1000 mL). The minimum inhibitory concentrations (MICs) of the test compounds were determined by a colorimetric method using the dye MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] [21]. A stock solution of the synthesized compound (50 μg/mL) in DMSO was prepared and graded quantities of the test compounds were incorporated in specified quantity of sterilized liquid MH medium. A specified quantity of the medium containing the compound was poured into microtitration plates. Suspension of the micro-organism was prepared to contain approximately 10^5 cfu/mL and applied to microtitration plates with serially diluted compounds in DMSO to be tested, and incubated at 37 °C for 24 h. After the MICs were visually determined on each of the microtitration plates, 50 μL of PBS (Phosphate Buffered Saline 0.01 mol/L, 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 of MTT/mL 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 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 550 nm. The observed MIC values are presented in table 3.

2.4. *Cytotoxicity*

The cytotoxicities against KB, K562, and Hep-G2 cells were evaluated as described elsewhere [22] with some modifications. Briefly, target tumor cells were grown to log phase in RPMI 1640 medium supplemented with 10% fetal bovine serum. After diluting to 2×10^4 cells mL^{-1} with the complete medium, 100 μL of the obtained cell suspension was added to each well of 96 well-cultured plates. The subsequent incubation was permitted at 37 °C, 5% CO_2 atmosphere for 24 h before cytotoxicity assessments. Tested samples at preset concentrations were added to 6 wells with 5-fluoruracil co-assayed as a positive reference. After 48 h exposure period, 40 μL of PBS containing 2.5 mg mL^{-1} of MTT was added to each well. Four hours later, 100 μL extraction solution (10% SDS-5% isobutyl alcohol-0.010 M HCl) was added. After an overnight incubation at 37 °C, the OD was measured at 570 nm on an ELISA microplate reader. In all experiments, three replicate

Table 3. MICs of the synthetic compounds.

	MICs (μg/mL)			
	Gram positive		Gram negative	
Compounds	*B. subtilis*	*S. aureus*	*E. coli*	*P. fluorescence*
Ligand	50	25	12.5	25
Zn(II) complex	6.25	6.25	1.56	3.13
Penicillin	0.78	3.13	>100	>100
Kanamycin	0.39	1.56	6.25	6.25

Table 4. Cytotoxic activities of the synthetic compounds.

	$IC_{50}/\mu M$		
Compounds	K562	KB	Hep-G2
Ligand	75.3 ± 4.5	64.6 ± 3.5	67.5 ± 2.8
Zn(II) complex	13.6 ± 1.5	8.6 ± 1.2	10.7 ± 0.8
5-Fluorouracil	13.4 ± 0.5	12.8 ± 0.6	14.6 ± 1.2

wells were used for each drug concentration. Each assay was carried out at least three times. The results are summarized in table 4.

3. Results and discussion

Zn(II) is four-coordinate by two N and two O from two Schiff-base ligands (figure 1). The geometry around Zn(II) can be described as a distorted tetrahedral geometry. The angles subtended at the Zn(II) atom range from 94.59(9)° to 125.11(14)°. The bond lengths of Zn–O (1.932(2) Å) and Zn–N (2.010(3) Å) are in the normal range [13]. Figure 2 gives the packing structure of the Zn(II) complex along the b-axis.

The synthesized Schiff base and its Zn(II) complex were screened for antibacterial activity against two gram (+) bacterial strains (*B. Subtilis*, and *S. aureus*) and two gram (−) bacterial strains (*E. coli* and *P. fluorescence*). The MICs of the compounds against these bacteria are presented in table 3. The antibiotics kanamycin and penicillin were included as reference. The results reveal that the Schiff base shows moderate activity

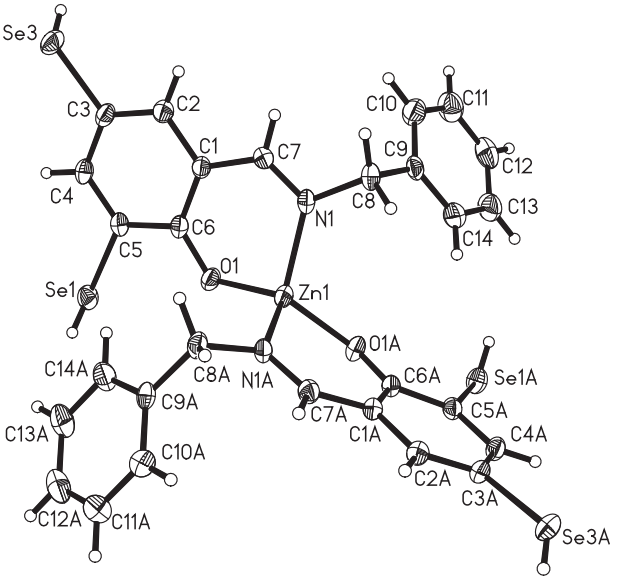


Figure 1. Crystal structure of Zn(II) complex, showing 30% probability displacement ellipsoids (arbitrary spheres for H).

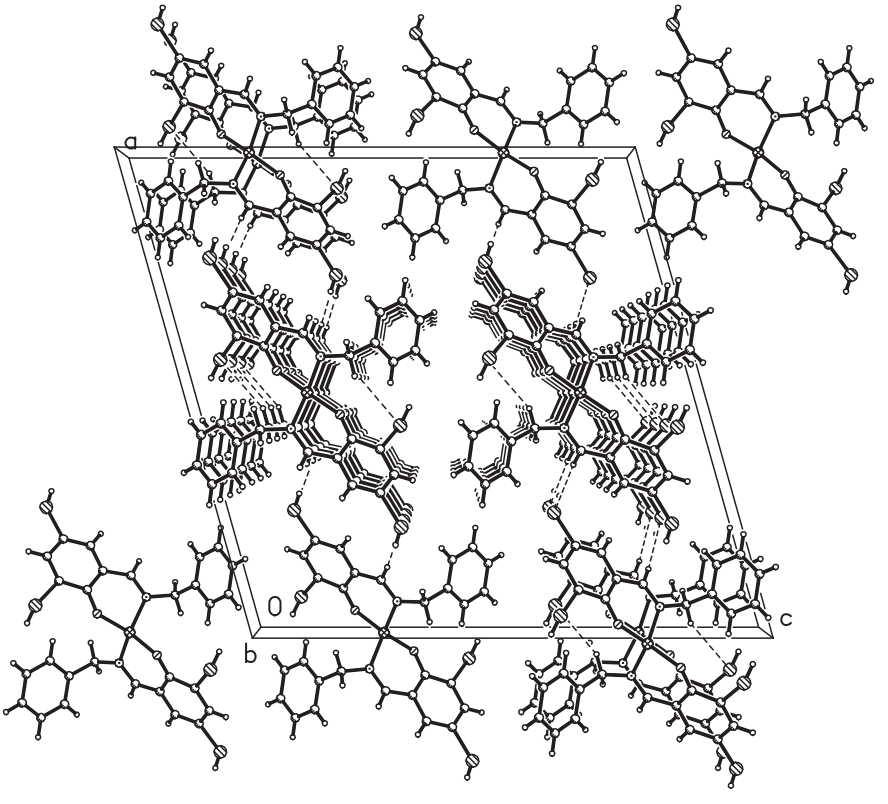


Figure 2. The packing structure of Zn(II) complex along the b-axis.

against the tested bacterial strains with the MIC from 12.5 to 50 μg/mL. Compared with the Schiff-base ligand, the Zn(II) complex shows more potent activities against the tested two gram (+) and two gram (−) bacteria, with the MIC range from 1.56 to 3.13 μg/mL, more potent than or similar with commercial antibiotics (kanamycin and penicillin).

The cytotoxic activities of the synthesized compounds against K562, KB, and Hep-G2 are summarized in table 4. The antitumor agent 5-fluoruracil was included as reference. The results indicate that the Zn(II) complex exhibits potent inhibitory activities against the tested tumor cell lines with IC_{50} ranged from 8.6 to 13.6 μM, which is more potent than or similar with 5-fluoruracil, while the Schiff-base ligand exhibits weak inhibitory activities against the three tumor cell lines with IC_{50} from 64.6 to 75.3 μM.

4. Conclusion

A Zn(II) complex with an organoselenium substituted Schiff-base ligand was synthesized and determined by X-ray diffraction analysis for the crystal structure. In the complex, the Zn(II) is four-coordinated by two phenolate O and two imine N from two ligands, forming a distorted tetrahedral geometry. The Zn(II) complex and its ligand were tested *in vitro* for their antibacterial and antitumor activity. Compared with other Zn(II) complexes reported recently [19, 23–29], this Zn(II) complex not only exhibits potent antitumor activities, but also displays favorable antibacterial activities.

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References

[1] S. Adsule, V. Barve, D. Chen, F. Ahmed, Q.P. Dou, S. Padhye, F.H. Sarkar. *J. Med. Chem.*, **49**, 7242 (2006).
[2] N. Shahabadi, S. Kashanian, F. Darabi. *Eur. J. Med. Chem.*, **45**, 4239 (2010).
[3] Z.H. Chohan, S.H. Sumrra, M.H. Youssoufi, T.B. Hadda. *Eur. J. Med. Chem.*, **45**, 2739 (2010).
[4] L. Shi, H.-M. Ge, S.-H. Tan, H.-Q. Li, Y.-C. Song, H.-L. Zhu, R.-X. Tan. *Eur. J. Med. Chem.*, **42**, 558 (2007).
[5] G. Kumar, S. Devi, R. Johari, D. Kumar. *Eur. J. Med. Chem.*, **52**, 269 (2012).
[6] G.H. Hegazy, H.I. Ali. *Bioorg. Med. Chem.*, **3**, 1259 (2012).
[7] M.S. Alam, J.-H. Choi, D.-U. Lee. *Bioorg. Med. Chem.*, **20**, 4103 (2012).
[8] K.E. Splan, A.M. Massari, G.A. Morris, S.S. Sun, E. Reina, S.T. Nguyen, J.T. Hupp. *Eur. J. Inorg. Chem.*, **12**, 2348 (2003).
[9] P.G. Cozzi, L.S. Dolci, A. Garelli, M. Montalti, L. Prodi, N. Zaccheroni. *New J. Chem.*, **27**, 692 (2003).
[10] M.E. Germain, T.R. Vargo, B.A. McClure, J.J. Rack, P.G. Van Patten, M. Odoi, M.J. Knapp. *Inorg. Chem.*, **47**, 6203 (2008).
[11] M. Poyraza, M. Sarıb, A. Güneya, F. Demircic, S. Demirayakd, E. Şahine. *J. Coord. Chem.*, **61**, 3276 (2008).
[12] M.T. Kaczmareka, R. Jastrząba, E. Hołderna-Kędziab, W. Radecka-Paryzek. *Inorg. Chim. Acta*, **362**, 3127 (2009).
[13] L. Shi, W.-J. Mao, Y. Yang, H.-L. Zhu. *J. Coord. Chem.*, **62**, 3471 (2009).
[14] X. Sheng, X. Guo, X.-M. Lu, G.-Y. Lu, Y. Shao, F. Liu, Q. Xu. *Bioconjugate Chem.*, **19**, 490 (2008).
[15] C. Yenikaya, M. Sari, M. Bülbül, H. Ilkimen, H. Celik, O. Büyükgüngör. *Bioorg. Med. Chem.*, **18**, 930 (2010).
[16] L. Lucia, V. Viera, B. Jela. *Toxicology*, **227**, 1 (2006).
[17] A.L. Mark, X. Shuling, L. Ganna, R.M. William. *Free Radical Biol. Med.*, **46**, 1527 (2009).
[18] S. Naira, V.K. Vermaa, C.S. Vermaa, T.A. Jaina, S.K. Tripathib, R. Singhc, S.K. Guptad, R.J. Butchere. *J. Coord. Chem.*, **63**, 4088 (2010).
[19] A.K. Asatkar, S. Nair, V.K. Verma, C.S. Verma, T.A. Jain, R. Singh, S.K. Gupta, R.J. Butcher. *J. Coord. Chem.*, **65**, 28 (2012).
[20] G.M. Sheldrick. *SHELX*-97, *Program for X-ray Crystal Structure Solution and Refinement*, Göttingen University, Germany (1997).
[21] J. Meletiadis, J.F. Meis, J.W. Mouton, J.P. Donnelly, P.E. Verweij. *J. Clin. Microbiol.*, **38**, 2949 (2000).
[22] X. Chen, C. Plasencia, Y. Hou, N. Neamati. *J. Med. Chem.*, **48**, 1098 (2005).
[23] H. Wu, J. Yuan, Y. Bai, G. Pan, H. Wang, J. Shao, J. Gao, Y. Wang. *J. Coord. Chem.*, **65**, 4237 (2012).
[24] Y.-F. Chen, M. Liu, J.-W. Mao, H.-T. Song, H. Zhou, Z.-Q. Pan. *J. Coord. Chem.*, **65**, 3413 (2012).
[25] H. Wu, Y. Bai, J. Yuan, H. Wang, G. Pan, X. Fan, J. Kong. *J. Coord. Chem.*, **65**, 2839 (2012).
[26] K. Pothiraj, T. Baskaran, N. Raman. *J. Coord. Chem.*, **65**, 2110 (2012).
[27] M. Jiang, Y.-T. Li, Z.-Y. Wu. *J. Coord. Chem.*, **65**, 1858 (2012).
[28] J. Lu, H. Guo, Y. Zhang, J. Jiang, Y. Liu, L. Zang, J. Huang. *J. Coord. Chem.*, **65**, 1765 (2012).
[29] B. Roopashree, V. Gayathri, H. Mukund. *J. Coord. Chem.*, **65**, 1354 (2012).