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ORIGINAL RESEARCH ARTICLE

Cd(II)–Salen Complex as a Potential Antimicrobial Agent: Synthesis and Experimental Evaluation

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Abstract

A tetranuclear cadmium(II) complex, $[Cd_4(L1)_2(\eta^1\text{-}NCS)_2(\mu_2\text{-}\eta^2{:}\eta^1\text{-}OAc)_2]$ (**C1**) (H_2L1 = *N*,*N*′-ethylene bis(3-methoxysalicylaldimine)), was synthesized and fully characterized by spectroscopic methods. The antimicrobial properties were assessed against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Candida albicans*. Complex **C1** displayed significantly improved antimicrobial activity relative to the free ligand, which may be attributed to the altered physicochemical properties upon coordination. These findings suggest that the Cd(II) complex is a promising candidate for further development as an antimicrobial agent.

1. INTRODUCTION

Cadmium is generally regarded as an environmental and biological hazard; however, it remains widely employed in applications such as rechargeable batteries, plastic pigments, and electroplated steel. Interestingly, the coordination of Cd(II) ions with various anions, including SCN^-, N_3^-, I^-, Br^-, and Cl^-, can significantly reduce its inherent toxicity while modulating its biological potential. In particular, Cd(II)–salen complexes incorporating suitable pseudo-halide linkers have demonstrated notable antimicrobial and anticancer activities. Nevertheless, prolonged exposure to cadmium at elevated levels is associated with severe health risks, especially liver and kidney damage, and has been

linked to increased cancer mortality.

In recent years, Cd(II)-based coordination complexes have attracted considerable attention due to their promising applications in catalysis, optical materials, supramolecular chemistry, clathrate formation, and advanced material science. Salen-type ligands, especially when combined with pseudo-halide groups, are highly favored for their strong chelating ability toward Cd(II) ions. Furthermore, metal-based drugs incorporating ONO-donor ligands with azomethine (–CH=N–) linkages have shown remarkable importance as drug carriers, antimicrobial agents, and imaging probes. The field of medicinal inorganic chemistry continues to expand, with significant research focused on metal complexes exhibiting diverse biological activities, including DNA binding, antimicrobial, anticancer, antiviral, antifungal, antimalarial, antitumor, and anti-inflammatory properties.

Notably, several M(II)–salen complexes have been explored as alternatives to conventional platinum-based chemotherapeutics such as cisplatin and carboplatin. However, these metal-based drugs often suffer from limitations, including nephrotoxicity, effects on gametogenesis, and neurotoxicity, necessitating the design of more targeted and safer compounds. In this context, the present study reports the synthesis, characterization, and antimicrobial evaluation of a Cd(II) complex, $[Cd_4(L1)_2(\eta^1\text{-}NCS)_2(\mu_2\text{-}\eta^2{:}\eta^1\text{-}OAc)_2]$ (**C1**), where H_2L1 = N,N'-ethylene bis(3-methoxysalicylaldimine).

2. EXPERIMENTAL

2.1 Materials and Methods

All chemicals and solvents employed in this study were of commercially available reagent grade and were used without further purification. Ethylenediamine and *o*-vanillin were procured from Sigma-Aldrich, while $Cd(OAc)_2{\cdot}2H_2O$, KSCN, and NaN_3 were obtained from E. Merck and SDFCL, India. Elemental (CHN) analyses were performed using a PerkinElmer 2400 elemental analyzer. FT-IR spectra were recorded in the range 4000–400 cm^{-1} using KBr pellets on a PerkinElmer RX 1 spectrophotometer, and Raman spectra were obtained on a Bruker RFS 27 instrument in the range 4000–50 cm^{-1}. ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker FT-NMR spectrometer operating at 300 MHz and 75.45 MHz, respectively, using tetramethylsilane (TMS) as an internal standard. UV–Visible spectra were measured in DMSO over the range 200–1100 nm using a Hitachi U-3501 spectrophotometer.

Caution! Cd(II) compounds are possibly poisonous. Hence, they ought to be prepared in small amounts and handled with care.

2.2 Synthesis of N,N'-Ethylene Bis(3-methoxysalicylaldimine)

N,N'-Ethylene bis(3-methoxysalicylaldimine) was synthesized by the condensation process [Majumdar et al., 2019] of 3-methoxysalicylaldehyde (0.152 g, 1 mmol) with ethylenediamine (0.0301 g, 0.5 mmol) in methanol (50 mL) at 80 °C for 3 h. The yellow crystalline solid separated out upon slow cooling. The yellow product was collected and air-dried under vacuum.

2.3 Synthesis of $[Cd_4(L1)_2(\eta^1\text{-}NCS)_2(\mu_2\text{-}\eta^2{:}\eta^1\text{-}OAc)_2]$ (C1)

To a methanol solution (15 mL) of cadmium acetate dihydrate (0.266 g, 1 mmol), a solution of the ligand (H_2L1) in methanol (10 mL) was added, followed by the dropwise addition of KSCN (0.097 g, 1 mmol) in a minimum volume of aqueous methanol with constant stirring for 2 h. Five drops of DMF were then added, and the solution was refluxed for 1.5 h at 65 °C. The yellow filtrate was cooled slowly and kept in a refrigerator for crystallization by slow evaporation. Yellow-coloured crystals were collected by filtration and completely air-dried.

2.4 X-ray Single-Crystal Diffraction

Single crystals of the Cd(II) complex suitable for X-ray diffraction were obtained via slow evaporation of a methanolic solution. Diffraction data were collected on a Bruker SMART CCD diffractometer using Mo Kα radiation ($\lambda = 0.71073$ Å) at 296–298 K. Data collection and reduction were performed using standard software packages, including SAINT and SADABS. The structure was solved and refined by full-matrix least-squares methods on F^2 using SHELXL-2014 as implemented in the OLEX2 program suite. All non-hydrogen atoms were refined anisotropically, whereas hydrogen atoms were placed in calculated positions and refined isotropically. Crystallographic figures were generated using DIAMOND (version 4.6.3) for the Supporting Information and MERCURY (version 2020.1) for the main manuscript. The crystallographic details are summarized in Table 1.

2.5 Antimicrobial Activity

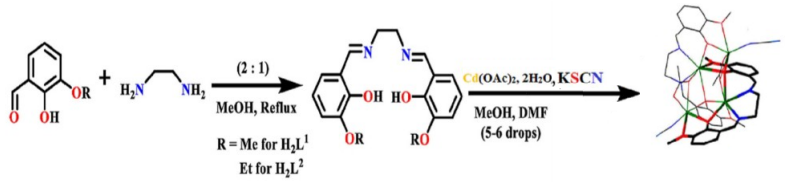
The synthesized compounds were tested for their *in vitro* antibacterial activity against the sensitive organisms *Staphylococcus aureus* (ATCC 25923), *Bacillus subtilis* (ATCC 6635), *Pseudomonas aeruginosa* (ATCC 27853), and *Escherichia coli* (ATCC 25922) using the Agar Well Diffusion method (for qualitative determination) and the serial dilutions in liquid broth method for determination of MIC values. All ATCC strains were procured from the American Type Culture Collection (ATCC, Manassas, VA, USA), and the media used in the study were purchased from Himedia, India. Each sample was inoculated with *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Candida albicans* and incubated at 37 °C overnight. The microbial turbidity was adjusted to be equivalent to a 0.5 McFarland turbidity standard. Thereafter, Mueller–Hinton agar plates (Merck, 105437) were swabbed uniformly with the standardized inoculum. Once the surfaces of the agar plates were dried aseptically, 6 mm wells were bored using a sterile cork-borer about two cm apart. The bottom of each well was coated with sterilized Mueller–Hinton agar at 45 °C. For each microorganism, separate samples of the ligands and compounds dissolved in DMSO were added into the wells and allowed to diffuse at room temperature for 2 h. Negative control (DMSO) and positive controls (Chloramphenicol and Nystatin) were included. The plates were incubated face upwards at 37 °C for 24 h. The diameters of the zones of inhibition were assessed utilizing a microscopic scale, and each experiment was conducted in triplicate. Data were analyzed by analysis of variance (ANOVA) using Origin Professional 8.5 statistical software, and mean contrasts were separated using Tukey's studentized test at the 1% level of significance.

3. RESULTS AND DISCUSSION

3.1 Characterization of the Salen-Type Ligand

The salen-type ligand was synthesized by the condensation of ethylenediamine with *o*-vanillin in MeOH at a 1:2 molar ratio.

***N*,*N*′-Ethylene bis(3-methoxysalicylaldimine) (H_2L1):** Yield: 0.145 g (88%). Anal. Calc. (Found) for $C_{18}H_{20}N_2O_4$: C, 65.84 (65.85); H, 6.14 (6.12); N, 8.53 (8.55)%. IR (KBr, cm^{-1}) selected bands: ν(C=N) 1632, ν(C–$O_{phenolic}$) 1249, ν(O–H) 3431. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm): 3.89 (s, 3H), 6.74–7.00 (m, 3H), 8.54 (s, 1H), 13.54 (s, 1H), 3.34–3.73 (s, 2H). ^{13}C NMR (DMSO-d_6, 75.45 MHz): δ (ppm): 56.07–58.81 (O–CH_3), 115.07–148.44 (Arom-C), 151.90 (C–OH), 167.58 (CH=N). UV–Vis (λ_{max}/nm): 332 nm.



Scheme 1. Syntheses of Salen ligand and Cd (II) complex

3.2 Characterization of Complex C1

Cd(II)-mediated complexes derived from *o*-vanillin condensed Schiff bases were prepared in moderate to good yield using a familiar *in situ* procedure [Bose et al., 2006, Agapiou et al., 2019]. A 1:1:1 molar ratio of cadmium acetate dihydrate, the ligand, and KSCN was dissolved in a minimum volume of aqueous methanol. The mixture was stirred and refluxed following the addition of a few drops of DMF (Scheme **??**). Yellowish block-shaped crystals of **C1** appeared at the junction of the solution phases after a few days (Figure 1).

The structure of **C1** was formulated as the discrete tetranuclear complex $[Cd_4(L1)_2(\eta^1\text{-NCS})_2(\mu_2\text{-}\eta^2\text{:}\eta^1\text{-OAc})_2]$. Yield: 0.712 g (53%). Anal. Calc. (Found) for $C_{42}H_{42}N_6O_{12}S_2Cd_4$: C, 37.74 (37.76); H, 3.17 (3.20); N, 6.29 (6.31)%. IR (KBr, cm^{-1}; w = weak; m = medium; s = strong; vs = very strong) selected bands: ν 2980 (w), 2880 (w), 2066 (vs), 2050 (w), 1634 (vs), 1560 (s), 1454 (vs), 1220 (s). FT-Raman (cm^{-1}) selected bands: 2932 (s), 2071 (vs), 1632 (vs), 1215 (s), 1468 (s). ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm): 8.49 ($1H_5$), 6.78–7.10 (m, $1H_2$, $1H_3$, $1H_4$), 3.76 ($2H_7$), 1.76 (CH_3COO^-). ^{13}C NMR (DMSO-d_6, 75.45 MHz): δ (ppm): 22.98 (–CH_3), 131.01 (Arom-C), 169.02 (C–OH), 177.75 (CH=N). UV–Vis (λ_{max} in DMSO): 370 nm.

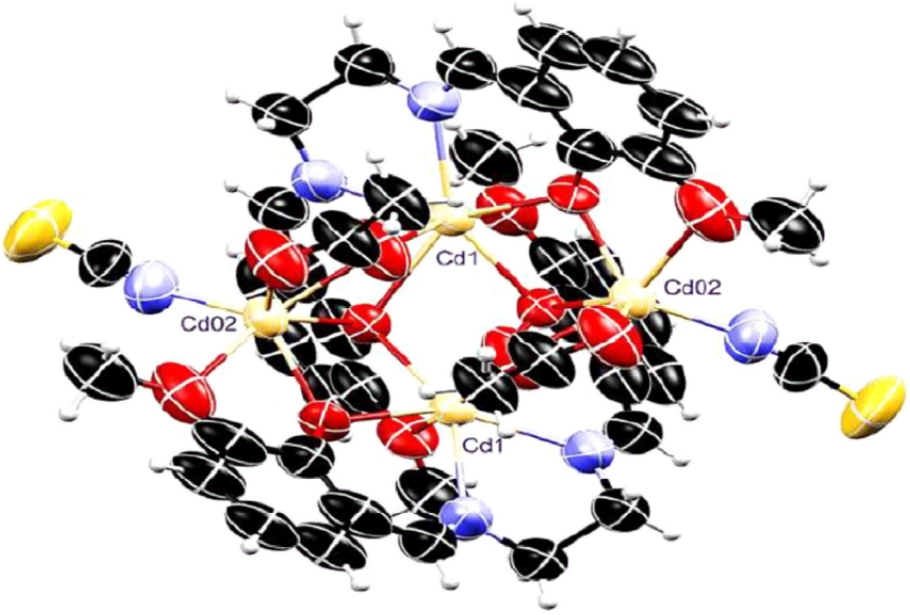


Figure 1. Yellowish block-shaped crystals of complex **C1** obtained by slow evaporation.

Table 1. Crystal data and structure refinement parameters for complex **C1**.

Parameter	Value
Formula	$C_{42}H_{42}N_6O_{12}S_2Cd_4$ (**C1**)
M / g mol^{-1}	1336.53
Crystal system	Orthorhombic
Space group	*Pbcn*
a / Å	20.7336(16)
b / Å	10.9976(9)
c / Å	21.3464(18)
α / °	90
β / °	90
γ / °	90
V / Å^3	4867(7)
Z	4
ρ_{calc} / g cm^{-3}	1.433
μ / mm^{-1}	1.874
$F(000)$	2624
Crystal size / mm^3	0.22 × 0.21 × 0.20
θ range / °	2.73 to 22.8
Limiting indices	$-24 \le h \le 23$, $-13 \le k \le 13$, $-20 \le l \le 25$
Reflections collected	54803
Independent reflections	4274 [$R_{int} = 0.1003$, $R_\sigma = 0.0409$]
Completeness to θ (%)	99.9
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4274 / 0 / 205
Goodness-of-fit on F^2	1.038
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0648$, $wR_2 = 0.1627$
R indices (all data)	$R_1 = 0.0931$, $wR_2 = 0.1787$
Largest diff. peak and hole / e Å^{-3}	1.43 and −1.06

3.3 Antibacterial and Antifungal Assay

The antimicrobial activity of the ligand (H_2L1) and complex **C1** was evaluated against two Gram-positive bacteria (*Staphylococcus aureus*, *Bacillus subtilis*), two Gram-negative bacteria (*Pseudomonas aeruginosa*, *Escherichia coli*), and one fungal strain (*Candida albicans*). The mean zone diameters and minimum inhibitory concentration (MIC) values are summarized in Tables 2 and 3, respectively.

The free ligand H_2L1 exhibited activity against all tested microorganisms except *Bacillus subtilis*, with notably good activity against *Staphylococcus aureus*. Complex **C1** demonstrated enhanced antimicrobial activity against all tested strains, particularly against *Candida albicans* (zone diameter: 30.0 mm) and moderate activity against *Pseudomonas aeruginosa*. Against *S. aureus*, both H_2L1 and **C1** showed moderate to high activity, consistent with reported trends for Cd(II)–Schiff base complexes [Roy et al., 2016, Musavi et al., 2017].

The MIC values of compounds exhibiting good antibacterial activity were determined to quantify

Table 2. Mean zone of inhibition (mm) for ligand H_2L1 and complex **C1** against selected microorganisms.

Compound	Gram-positive		Gram-negative		Fungus
	S. aureus	*B. subtilis*	*P. aeruginosa*	*E. coli*	*C. albicans*
H_2L1	19.3 ± 0.3	–	14.1 ± 0.3	16.3 ± 0.2	9.9 ± 0.4
C1	18.4 ± 0.4	18.6 ± 0.3	21.6 ± 0.2	20.7 ± 0.3	30.0 ± 0.4
Chloramphenicol	26.0 ± 0.4	24.0 ± 0.3	22.0 ± 0.1	25.0 ± 0.2	–
Nystatin	–	–	–	–	19.0 ± 0.1
DMSO (control)	–	–	–	–	–

Each value represents mean ± standard deviation (SD) of six replicates. "–" indicates no detectable inhibition.

potency. The enhanced activity of **C1** against Gram-positive strains may be attributed to the increased lipophilicity of the metal complex upon coordination, facilitating better penetration through microbial cell membranes [Devi and Pachwania, 2018]. This observation aligns with prior reports on Cd(II)–salen systems [Das et al., 2017, Majumder et al., 2017].

Table 3. Minimum inhibitory concentration (MIC) values of complex **C1** against selected bacterial strains.

Compound	MIC (μg/mL)	
	S. aureus	*P. aeruginosa*
C1	15.3	61.4
Chloramphenicol	>5	>5

Lower MIC values denote higher antimicrobial potency.

4. CONCLUSION

A salen-based ligand (H_2L1) and its tetranuclear Cd(II) complex, $[Cd_4(L1)_2(\eta^1\text{-NCS})_2(\mu_2\text{-}\eta^2{:}\eta^1\text{-OAc})_2]$ (**C1**), were successfully synthesized and comprehensively characterized using FT-IR, FT-Raman, UV–Vis, and $^1H/^{13}C$ NMR spectroscopic techniques. The IR and Raman spectral data confirmed the bridging coordination mode of the NCS^- co-ligand. The ^1H NMR spectra exhibited a downfield shift of the azomethine (–CH=N–) proton, indicating coordination of the imine nitrogen to the Cd(II) center, which was further corroborated by the corresponding shift observed for the azomethine carbon in the ^{13}C NMR spectra.

The antimicrobial evaluation revealed that complex **C1** exhibits significantly enhanced activity relative to the free ligand against both bacterial and fungal strains, with particularly promising results against *Candida albicans* and Gram-positive *Staphylococcus aureus*. These findings underscore the potential of Cd(II)–salen complexes as viable candidates for the development of novel metal-based antimicrobial agents [Palanisami and Moon, 2014, Zhou et al., 2015]. Future work will focus on mechanistic studies, cytotoxicity profiling, and structure–activity relationship analyses to further optimize these complexes for biomedical applications.

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