**Research Article** 

# Synthesis, characterization, biological screening and determination of stability constants of *N*,*N*'-Bis[1-(4-chlorophenyl)ethylidene] ethane-1,2-diamine



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#### Abstract

A Schiff base ligand, *N*,*N*'-bis[1-(4-chlorophenyl)ethylidene]ethane-1,2-diamine (**SBL**), was synthesized by condensation of 4-chloroacetophenone with ethylenediamine in methanol in the presence of  $H_2SO_4$  as catalyst. The structure of **SBL** was elucidated by spectroscopic (<sup>1</sup>H-NMR, <sup>13</sup>C-NMR, IR and MS) and elemental analyses, and also confirmed by XRD. The **SBL** was used to prepare metal complexes **1-2** with Pb<sup>+2</sup> and Cd<sup>+2</sup>, respectively. The structures of the complexes were elucidated by IR, MS and elemental analyses. On the basis of electronic spectra and magnetic moment data, octahedral geometry was proposed for the synthesized complexes **1-2**. The conductivity data showed the non-electrolytic nature of the complexes **1-2**. The **SBL** and complexes **1-2** were subjected to measure their biological potential against *Staphylococcus aureus, Bacillus subtilis* and *Escherichia coli* bacteria. **SBL** showed non-significant anti-bacterial potential whereas complexes showed more toxic effect than the **SBL**. In the experiments to determine the stability constants of **SBL** with Cu(OAc)<sub>2</sub>, CoCl<sub>2</sub> and Co(NO<sub>3</sub>)<sub>2</sub>; **SBL** showed highest stability constants with Cu(OAc)<sub>2</sub> which is 1.550 × 10<sup>7</sup> at 1:1 (L:M) and second highest with Co(NO<sub>3</sub>)<sub>2</sub> which is 6.861 × 10<sup>6</sup> at 3:2 (L:M).

**Keywords** Schiff base ligands · Complexes · Synthesis and structure elucidation · Stability constants · Antibacterial and toxicity potentials · Brine shrimp assay

JEL Classification 120 · 123

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### 1 Introduction

Schiff bases are c=N — containing organic species and excellent ligands to form metal complexes [1]. They can be efficiently synthesized by the condensation of aldehydes/ ketones with primary amines and easily employed to form metal complexes [2] which show better biological

activities and low cytotoxic effects as compared to parent ligand [3]. The importance of Schiff bases can be estimated as they use in biological systems for transamination and elucidation of racemization mechanisms [4]. Along with these facts, imine bond is considered responsible for various biological activities, such as antimicrobial, anticonvulsant, anti-inflammatory, antitumor [5–8], herbicidal [9],

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antituberculosis, anti-HIV activities and etc. [10, 11]. Due to versatile uses of Schiff bases, they have engrossed much attention and prompted us to synthesize and characterize a Schiff base ligand, *N*,*N*'-bis[1-(4-chlorophenyl)ethyl-idene]ethane-1,2-diamine (**SBL**), and its Pb(II) and Cd(II) metal complexes (**1-2**). The products were further subjected to measure their antibacterial and toxicity potential, including stability constant of **SBL**.

# 2 Experimental work

# 2.1 Material and methods

The chemicals used for the synthesis were purchased from BDH/Merck and used without any further purification. The metal salts used for the synthesis were hydrated of metal (II) acetate. Pre-coated silica gel plates G-25-UV<sub>254</sub> were used for conducting TLC and detection was done at 254 and 366 nm. Mettler Toledo electric balance was used for weighing. Thermo Nicolet Avatar 320 FTIR spectrometer was used to measure IR spectra through KBr pellets. Specord 200 UV-VIS spectrophotometer was used for measuring UV-VIS spectra. Melting points were determined on Gallenkamp apparatus and are uncorrected. Perkin Elmer 2400 Series II elemental analyzer was used for elemental analyses and Jenway 4010 was used for measuring molar conductance at room temperature in DMSO  $(1 \times 10^{-3} \text{ M})$ . Moreover, Guy-type magnetic balance (Hertz SG8SHJ) was employed for the measurement of the magnetic moment. JEOL SX102/DA-6000 mass spectrometer was used to measure mass spectra by using glycerol as matrix and mass is given in m/z (%). The <sup>1</sup>H- and <sup>13</sup>C-NMR spectra were recorded on a Bruker AMX-400 spectrometer in DMSO- $d_6$ . The chemical shifts ( $\delta$ ) are given in ppm, relative to tetramethylsilane as an internal standard, and the scalar coupling constants (J) are reported in Hertz.

# 2.2 Procedure of synthesis of Schiff base (SBL)

4-Chloroacetophenone (0.2 mol in 30 ml MeOH) and ethylenediamine (0.1 mol in 30 ml MeOH) were refluxed together at 90  $^{\circ}$ C on water bath for 4 h. After refluxing the reaction mixture, the solvent was evaporated on a

Fig. 1 Synthesis of Schiff base ligand (SBL)

rotary evaporator up to one third of its initial volume, then acetone was added and placed in ice bath. The off white crystals of Schiff base ligand (**SBL**) were obtained by placing the resulting mixture for overnight at room temperature. The product was filtered and washed with cold methanol (methanol at ambient temperature), and recrystallized with methanol. The crystals were dried by keeping at reduced pressure on anhydrous CaCl<sub>2</sub> for 12 h. TLC was used to check the purity (Fig. 1).

# 2.3 N,N'-Bis[1-(4-chlorophenyl)ethylidene] ethane-1,2-diamine (SBL)

Off-white crystals; yield: 75%; m.p. 168 °C; Anal. Calcd. for  $C_{18}H_{18}Cl_2N_2$ : C 64.91, H 5.58, N 8.52. Found: C 64.87, H 5.54, N 8.41; IR (KBr): 2850 (C–H), 1625 (C=N), 1601–1410 (benzene ring) cm<sup>-1</sup>; <sup>1</sup>H-NMR (300 MHz, DMSO- $d_6$ )  $\delta$ : 7.81 (4H, d, J=8.7 Hz, H-5, -9, -14, -18), 7.43 (4H, d, J=8.7 Hz, H-6, -8, -15, -17), 3.79 (4H, s, H-10, -19), 2.22 (6H, s, H-4, -20); <sup>13</sup>C-NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ /ppm): 163.7 (C-2, -12), 139.2 (C-3, -13), 134.1 (C-7, -16), 128.1 (C-6, -8, -15, -17), 128.0 (C-5, -9, -14, -18), 52.7 (C-10, -19), 15.1 (C-4, -20); FABMS (m/z): 333.1 [M+H]<sup>+</sup>.

# 2.4 General procedure for the synthesis of metal complexes (1-2)

The methanolic solution of metal salt [(Pb(CH<sub>3</sub>COO)<sub>2</sub>.3H<sub>2</sub>O or Cd(CH<sub>3</sub>COO)<sub>2</sub>.2H<sub>2</sub>O] was added to a hot methanolic solution of ligand (**SBL**) with the molar ratio 1:2 (M:L) and refluxed for 45 min in boiling methanol. For complex formation, the medium was basified by drop wise adding of 1 N NaOH in MeOH. The complex products **1-2** (Fig. 2) were filtered off and washed with cold methanol and dried over anhydrous CaCl<sub>2</sub> under vacuum.

### 2.4.1 [Pb(BSL)<sub>2</sub>(OAc)<sub>2</sub>](1)

Pale yellow solid; yield: 61%; m.p. 347 °C (decomp.); Anal. Calcd. for  $C_{40}H_{42}Cl_4N_4O_4Pb$ : C 48.52, H 4.32, N 5.51, Pb 20.81. Found: C 48.48, H 4.27, N 5.55, Pb 20.89; IR (KBr, cm<sup>-1</sup>): 2888 (C-H), 1633 (COO)<sub>as</sub>, 1562 (C = N), 1598 & 1438 (benzene ring), 1272 (COO)<sub>s</sub>, 453 (Pb-N); Molar



*N,N*'-Bis[1-(4-chlorophenyl)ethylidene]ethane-1,2-diamine (**SBL**)

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Fig. 2 Proposed structures of complexes (1-2)

conductance (DMSO)  $\lambda$ m (Ohm<sup>-1</sup>cm<sup>2</sup>mol<sup>-1</sup>): 3.1; MS (*m/z*): 991.1 [M + H]<sup>+</sup>; Magnetic moment,  $\mu_{eff}$ ,  $\mu$ B: 5.17.

### 2.4.2 $[Cd(BSL)_2(H_2O)_2](2)$

Light yellow solid; yield: 61%; m.p. 210 °C (decomp.); Anal. Calcd. for  $C_{36}H_{40}Cl_4N_4O_2Cd$ : C 53.12, H 4.98, N 6.90, Cd 13.81. Found: C 53.06, H 4.95, N 6.87, Cd 13.79; IR (KBr)  $\upsilon$  (cm<sup>-1</sup>): 3549 (O–H), 2936 (C–H), 1568 (C=N), 1600 and 1480 (benzene ring), 491 (Cd–N); Molar conductance (DMSO)  $\lambda_m$  (Ohm<sup>-1</sup>cm<sup>2</sup>mol<sup>-1</sup>): 4.3; FABMS (*m/z*): 815.0 [M+H]<sup>+</sup>; Magnetic moment,  $\mu_{eff}$  µB: 5.40.

### 2.5 Biological assays

#### 2.5.1 Antibacterial assay

The antibacterial potential of **SBL** and its complexes **1-2** was measured against *Staphylococcus aureus, Escherichia coli* and *Bacillus subtilis* bacteria. The petri plates were sterilized and 10 mL of nutrient medium (*i.e.* agar) was poured into the petri dishes and allowed it to solidify. Spore suspensions of bacteria were used for inoculation of plates. Sterilized cork borer were used for making wells in the center of plates. The solutions (0.5 mL) of under estimated compounds were poured into already prepared wells. The plates were inoculated at 37 °C and after 24 h, zone of inhibition produced in each plate around the respective wells was measured. The standard used for this purpose was impinium.

#### 2.5.2 Brine shrimp assay

The artificial sea water was prepared by dissolving 3.8 g sea salt in double distilled and filtered water. The shrimp eggs (i.e. 1 mg Artermia salina) were added to the small tank of sea water. The partitions of tank, having these eggs, were covered and darken with aluminium foil. The illumination of perforation in the dam was employed to attract the shrimp larvaes. The hatching and maturity of shrimps were carried out by allowing it to stand for 24 h at 25 °C. After two days, the mature shrimp larvae were ready. The test compounds were dissolved in DMSO to prepare samples of different concentrations (50, 100 and 150 mg/mL). As a result, 18 vials were prepared by making triplicate of each sample. 12 shrimps and 5 mL of sea water was added in each sample vial and then allowed to stay for 24 h under illumination. The data for shrimp lethality was analyzed by employing Finney computer programme and LD<sub>50</sub> values were determined by counting the number of surviving shrimps [12, 13].

#### 2.6 Determination of stability constants

Stock solutions  $(1 \times 10^{-3} \text{ M})$  of Cu(II), Co(II) and **SBL** were prepared in methanol. Stock solutions of ligand and metal were mixed in different proportions. Each proportion contained total volume as 10 mL. Stability constants were determined at  $\lambda_{max}$  of the ligands. Stability constants of *N*,*N*'-bis[1-(4-chlorophenyl)ethylidene]ethane-1,2-diamine with Cu(II) and Co(II) were determined by Job's method of continuous variation by using visible spectrophotometer. The formula to determine stability constants is shown below:

$$k_{s} = \frac{(A/Aex)C'}{\left[\left(Cm - \left(\frac{A}{Aex}\right)C'\right)\left(Cx - \left(\frac{A}{Aex}\right)C'\right)\right]}$$

where

A = absorbance peak. Aex = extraploted absorbance. Cm = concentration of metal. C' = concentration of complex. Cx = concentration of ligand.

### **3** Results and discussion

*N*,*N*'-Bis[1-(4-chlorophenyl)ethylidene]ethane-1,2-diamine (**SBL**) was synthesized in the form of crystalline solid with off-white colour which was insoluble in water and soluble in most common organic solvents except ether. The

metal complexes **1-2** of the **SBL** were prepared in the form of solids and the decomposition temperatures of these complexes reflect the fact that they are literally stable compounds. However, the solubility behavior of these complexes is different from the Schiff base ligand as these are insoluble in water and most common organic solvents except DMF and DMSO.

# 3.1 FAB mass spectra

The mass spectra of **SBL** and complexes **1-2** were analyzed by the FAB (positive). The pseudo molecular ion peak  $[M+H]^+$  at m/z 333.1, indicated free **SBL** and confirmed the theoretical molecular weight which is 332.0. The stoichiometry of metal to ligand in the ratio 1:2 was supported by the observed molecular ion peaks in the spectra of complexes. The data of mass spectra were found in complete agreement to that of obtained via elemental analysis.

# 3.2 Infrared spectra

The binding mode of Schiff base ligand (SBL) to metal in the complexes 1-2 was studied by comparison of IR spectra of **SBL** and metal complexes. The disappearance of characteristic bands of carbonyl group, v(C=O) for free 4-chloroacetophenone and peaks for N–H str.  $v(-NH_2)$ of free ethylenediamine suggested that the reaction is complete and no unreacted ketone or amine are left [14] Moreover, the azomethine band of **SBL** at 1625 cm<sup>-1</sup> underwent a shift towards the lower frequency region at 1556–1569 cm<sup>-1</sup> due to complexation of ligand with metal ion. This observation further indicated that the nitrogen atom of azomethine group is involved in coordination with metal atom and it can be described by the fact that empty *d*-orbitals of the metal atom accept the electron pair available on the nitrogen atom of azomethine group [15], a medium intensity band at 409–491 cm<sup>-1</sup> assignable to v(M-N) [16] in both complexes, further confirmed the complexation.

The bands in the region of 1400–1480 cm<sup>-1</sup> and 1031–1099 cm<sup>-1</sup> v(C=C) were assigned to stretching vibrations of the aromatic ring system. The acetate complexes (1) showed absorption bands at 1633 and 1681 cm<sup>-1</sup> which were assigned to the v(COO<sup>-</sup>)<sub>as</sub> (i.e. asymmetric stretching vibrations of the acetate ion) and the bands observed at 1272 and 1278 cm<sup>-1</sup> in acetate complexes were assigned to symmetric stretching vibration v(COO<sup>-</sup>)<sub>s</sub> of acetate ion, which indicated that the coordination of acetate group in a unidentate manner to central metal ion (Fig. 2).

The stretching vibration v(C-H) of the methyl group of the ligand and complexes were assigned to the bands in the region of 2850–3087 cm<sup>-1</sup>. The presence of coordinated water in complex **2** was suggested by the broad band present at 3549 cm<sup>-1</sup> (Fig. 2) [17, 18].

#### 3.3 Electronic spectra and magnetic moments

The position, number of d-d transitions and charge transfer formed the basis for stereochemistry of metal ions in complexes **1-2** and stereochemistry was assigned by observing electronic spectra. The octahedral geometry was suggested for the complexes [19] by observing electronic spectra and magnetic moment values (Table 1), which was further strengthened by the low value of molar conductance, indicating the nature of complexes as non-electrolytic.

### 3.4 Molar conductance

The molar conductivities of the complexes **1-2** were measured at ambient temperature by dissolving them in DMSO  $(1 \times 10^{-3} \text{ M})$ . The complexes **1-2** were found to have molar conductance values in the range of  $3.1-5.2 \Omega^{-1} \text{ cm}^2 \text{ mol}^{-1}$ , which indicates the non-electrolytic nature of the complexes [20].

The tentative proposed structures of the complexes **1-2** are illustrated in Fig. 2, which can be analyzed easily in the light of analytical and spectral data.

## 3.5 Crystallographic studies

*Crystal data*: **(SBL**), C<sub>18</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>2</sub>, Mr = 33.24 g.mol<sup>-1</sup>, white rod like, 0.31, 0.11, 0.08 mm<sup>3</sup>, monoclinic, space group  $P2_1/c$ , a = 4.3427(2), b = 10.1489(5), c = 18.9213(8) Å,  $\beta = 91.458(1)^\circ$ , V = 833.67(5), Z = 2, Dc = 1.328 g.cm<sup>-3</sup>, *F*(000) = 348, MoKα radition,  $\lambda = 0.71073$  Å, T = 296 (2) K, 2θmax = 54.0°, 7719 reflection collected, 2071 unique (R<sub>int</sub> = 0.021), Final GooF = 1.083, R<sub>1</sub> = 0.042, wR<sub>2</sub> = 1.03, R indices based on 1405 reflections with I > 2σ(I) (refinement on F2) 101 parameters, Lp and absorption correction applied,  $\mu = 0.39$  mm<sup>-1</sup>.

*Refinement*: KAPPA APEX II diffractometer (Bruker) was used to collect the data under the mentioned conditioned. Cell refinement and data reduction was carried out using SAINT [21] while structure solution and refinement was done using SHELXS-97 [22]. PLATON [23] and WinGX [24]

 Table 1
 Electronic and magnetic moment data of complexes 1-2

Compound	Electronic spectra wavelength (cm <sup>-1</sup> )	Magnetic moment (B.M.)	Geometry
1	9400, 13,450, 197,500	5.17	Octahedral
2	21,350, 28,500	5.40	Octahedral

were used for molecular graphics. In the refinement procedure, all the non-hydrogen atoms were refined with anisotropic displacement parameters. The aromatic and aliphatic C–H hydrogen atoms were positioned geometrically and refined as riding atom over their parent carbon atoms.

The ligand was crystalized with centro-symmetric space group to study three dimensional behavior of molecule. Crystal structure reveals that molecule gained crystallographic inversion symmetry position in unit cell. The central backbone of molecule is oriented at dihedral angle of 19.26 (12)° with respect to the aromatic ring (Fig. 3). Trans conformation has been observed around the two C=N double bonds. The root mean square deviation values of the atoms C7, C8, N1 and C9 from the plane generated through the C1–C6 are 0.072 (3)°, – 0.326 (4)°, 0.465 (3)° and 0.562 (4)° respectively. Molecule does not show any type of hydrogen bonding or  $\pi$ – $\pi$  interaction.

#### 3.6 Stability constants

Stability constants of Schiff base ligand (SBL) with copper and cobalt were determined by Job's method of continuous variation using UV-Visible spectrophotometer at  $\lambda_{max}$  320 nm. The product was soluble in organic solvents but insoluble in distilled water. Stability constants of Schiff base ligand with copper chloride were determined as  $6.336 \times 10^4$  at 2:1 (L:M) and  $2.017 \times 10^5$  at 1:1 (L:M) and their log values were found as 4.802 and 5.305, respectively. Stability constant of Schiff base with copper acetate was determined as  $1.550 \times 10^7$  at 1:1 (L:M) and its log value was calculated as 7.190. Stability constant of Schiff base with cobalt chloride was found as  $1.335 \times 10^{6}$ at 1:1 (L:M) and its log value as 6.125. Stability constants of Schiff base with cobalt nitrate were determined as  $6.861 \times 10^{6}$  at 3:2 (L:M) and  $2.450 \times 10^{6}$  at 1:4 (L:M) and their log values were found as 6.836 and 6.389, respectively. Consequently, in case of Cu<sup>2+</sup>, **SBL** showed highest stability constant with copper acetate at 1:1 (L:M) which is  $1.550 \times 10^7$  whereas in case of Co<sup>2+</sup>, **SBL** showed highest stability constant with cobalt nitrate at 3:2 (L:M) which is  $6.861 \times 10^6$ . As a whole, the stability constant order is  $1.550 \times 10^7$  at 1:1 (L:M) with Cu(OAc)<sub>2</sub> >  $6.861 \times 10^6$  at 3:2 (L:M) with Co(NO<sub>3</sub>)<sub>2</sub> >  $2.450 \times 10^6$  at 1:4 (L:M) with Co(NO<sub>3</sub>)<sub>2</sub> >  $1.335 \times 10^6$  at 1:1 (L:M) with CoCl<sub>2</sub> >  $2.017 \times 10^5$  at 1:1 (L:M) with CuCl<sub>2</sub> >  $6.336 \times 10^4$  at 2:1 (L:M) with CuCl<sub>2</sub>. Stability constants determined that acetate of copper was more stable than chloride of copper whereas nitrate of cobalt was found more stable than chloride of cobalt with Schiff base (Fig. 4, Table 2).

#### 3.7 Biological activities

#### 3.7.1 Antibacterial activity

The agar plate technique was used to measure the antibacterial potential of Schiff base ligand (SBL) and its complexes 1-2 against S. aureus, E. coli and B. subtilis bacteria, and results are shown in Table 3. The studies were conducted by using 1% solution of compounds. The result showed that the **SBL** showed non-significant potential and less active than the metal chelates 1-2 which showed moderate potential against all strains. These facts can be explained by Tweeedy's chelation theory [25], in chelation ligand sharing its electrons with metal ion and reduces polarity of metal ion. The reduction of polarity enhances penetration of complexes into the lipid membrane and causes blockage of binding sites in the enzymes of pathogens. The phenomenon of protein synthesis is blocked by interference of complexes with the respiration processes of cell and as a result further growth of pathogens is restricted.

#### 3.7.2 Brine shrimp assay

The convenient way to evaluate new bioactive synthetic products is to monitor in vivo lethality to shrimp larvae because new bioactive compounds are often cytotoxic

Fig. 3 Labelled diagram of SBL with thermal ellipsoids drawn at 50% probability



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Fig. 4 Stability constants of SBL with CuCl<sub>2</sub>, Cu(OAc)<sub>2</sub>, CoCl<sub>2</sub> and Co(NO<sub>3</sub>)<sub>2</sub>

Table 2 Stability Constants of Schiff base with  $Cu^{2+}$  and  $Co^{2+}$ 

S. No	Metals	L:M	Ks	Log K <sub>s</sub>
1	CuCl <sub>2</sub> .2H <sub>2</sub> O	2:1	6.336×10 <sup>4</sup>	4.802
		1:1	$2.017 \times 10^{5}$	5.305
2	Cu(CH <sub>3</sub> COO) <sub>2</sub> .H <sub>2</sub> O	1:1	$1.550 \times 10^{7}$	7.190
3	CoCl <sub>2</sub> .6H <sub>2</sub> O	1:1	$1.335 \times 10^{6}$	6.125
4	Co(NO <sub>3</sub> ) <sub>2</sub> .6H <sub>2</sub> O	3:2	$6.861 \times 10^{6}$	6.836
		1:4	$2.450 \times 10^{6}$	6.389

Table 3 Antibacterial activity of ligand (SBL) and complexes (1-2)

Compound	Diameter of ir	ım)	
	S. aureus	E. coli	B. subtilis
L	2	1	2
1	4	4	6
2	5	4	4
Impinium*	8	7	11

\*Standards

to shrimp larvae. Such type of bioassay is quick and economical in general and further in vivo animal experiments on larger scale are based on this intermediary test. Brine shrimp lethality test was used to determine the

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# **4** Conclusions

A Schiff base, *N*,*N'*-Bis[1-(4-chlorophenyl)ethylidene] ethane-1,2-diamine (**SBL**) and its complexes with Pb<sup>2+</sup> and Cd<sup>2+</sup> were synthesized in good yield and characterized by spectroscopic data. The **SBL** was inactive whereas metal complexes **1-2** were moderately active against selected bacteria, complexes were more cytotoxic that the parent Schiff base and complexes were of non-electrolytic nature. In the stability constant experiments, **SBL** showed highest stability constant with Cu(OAc)<sub>2</sub> at 1:1 (L:M) ratio.

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#### **Compliance with ethical standards**

Conflict of interest Authors not have any conflict of interests.

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