Antibacterial activity of some Salen metal complexes

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Abstract:
This article primarily designed to determine antibiotic features of new species of Schiff base metal complexes [(MCl\(_2\))\(_2\)(Salen)] (M = Co (1), Ni (2), Cu (3), Sn (4), Ba (5), Salen = 1,2-Bis(salicyldenamino)ethane. Five binuclear complexes were synthesised by direct reaction of the corresponding metal chloride (CoCl\(_2\), NiCl\(_2\), CuCl\(_2\), SnCl\(_2\), and BaCl\(_2\)) with the Schiff base ligand. Obtained Salen metal complexes characterised by, FT-IR and \(^1\)H-NMR, and mass spectra, spectra studies suggests that Schiff base ligand behaves as dimetalic N bidentate at metal centres. Also, these Salen complexes were tested for antibacterial activity using the Broth dilution method against two strains of gram negative bacteria (\textit{E coli G-} and \textit{Klebsiella G-}).

Introduction
Antibiotic resistance is a growing challenge that promotes researchers to explorer new antibiotic species.[36 ] Over several decades Schiff base ligand system continues attracting inorganic chemists’ attention. Due to chelating and tunable features that can provide an excellent cag to coordinate to the metal centre.[1] It is well known that coordinating ligands containing polar atoms such as O and N show wide antibacterial range.[2] Moreover, scientists notice such activity can be increase dramatically when such ligands coordinated with metal.[3, 4] Previous studies extensively reported a wide range of medicinal features of Schiff bases. For example, antibacterial [5, 6], antifungal [7], antitumor [8], antiviral [9], anti-HIV [10], herbicidal [11] and anti-influenza.[12] Moreover, a wide range of industrial applications has reported in catalysis and material chemistry. Furthermore, photoluminescence features of Salen metal complexes employed successfully in medical diagnostics, cell biology, and environmental sciences.[13]
Continuing our studies on synthesis, structural determination of homodinuclear $M^{II}$ Schiff base metal complexes and their antibacterial activity, we herein describe the preparation, analytical and spectroscopic characterization of $[(MCl_2)_2(Salen)]$ ($M = \text{Co (1)}, \text{Ni (2)}, \text{Cu (3)}, \text{Sn (4)}, \text{Ba (5)}$) complexes containing the N, O-donor ligand derived from salicylaldehyde and ethane-diamine. The antibiotic activity of the complexes towards $\text{(E coli G- and Klebsiella G-)}$ in vitro has been investigated according to the broth dilution method.

**Chemical materials and experimental methods**

All the glassware used for synthesis were cleaned with HCl, distilled water and then dried in the oven at 110 °C. All the chemicals were obtained from Sigma Aldrich were of analytical grade and used without further purification. FT-IR spectra (KBr discs) (4000-200 cm$^{-1}$) were recorded on FT-IR Spectrometer (Bruker). Proton NMR spectra were recorded in DMSO-d6. Chemical shifts (δ) are expressed in parts per million downfield using tetramethylsilane as an internal reference or by using the residual protonated solvent on Varian 400 NMR spectrometer. Mass spectra of the compounds were recorded on Agilent Technology (HP) 5973 Network Mass Selective Detector. NMR and Mass analyses were done at Central Instrumental Lab., School of Chemistry, College of Science, University of Tehran, Enghelab St., Tehran, Iran.

**Salen proligand synthesis**

Condensation reaction [14] was employed to synthesise Schiff base proligand (Salen). This method involved dissolving salicylaldehyde (0.13 g, 1 mmol) and (1,2-ethane-diamine) (0.12 g, 2 mmol) in 25 ml methanol in a round bottomed flask (50 ml) equipped with a condenser (Eqn. 1). The reaction mixture was stimulated by droplets of acetic acid, refluxed and stirred for 4 hours then the reaction mixture was cooled, filtered and dried in a desiccator over anhydrous CaCl$_2$ and recrystallized from methanol, a sharp orange crystalline product was obtained.

**Equation 1**

**Salen metal complexes syntheses**

CoCl$_2$, NiCl$_2$, CuCl$_2$, SnCl$_2$, BaCl$_2$ salts were reacted with Schiff base form solid complexes $[(\text{CoCl}_2)_2(\text{Salen})]$ (1), $[(\text{NiCl}_2)_2(\text{Salen})]$ (2), $[(\text{CuCl}_2)_2(\text{Salen})]$ (3), $[(\text{SnCl}_2)_2(\text{Salen})]$ (4) and $[(\text{BaCl}_2)_2(\text{Salen})]$ (5) (Eqn. 2). These complexes were prepared by addition of (2 mmol, 0.25 g CoCl$_2$, 0.25 g NiCl$_2$, 0.26 g CuCl$_2$, 0.37 g SnCl$_2$, 0.41 g BaCl$_2$) $MCl_2$ in about 25 mL ethanol to a hot solution of (1 mmol, 0.26 g) Salen in about 15 mL ethanol with continuous stirring. The
reaction mixture was refluxed for 4 hours. Colored complexes precipitates were filtered, washed with methanol, and dried in a vacuum desiccator.

Equation 2

\[
\text{Biological activity}
\]

Anti-bacterial activities of the chemical compounds (1-5) were screened in vitro using disc diffusion method. The strains were treated with compounds 1-5 which were dissolved in distilled water. Biological activity of these compounds were tested against two strains of gram negative bacteria (E. coli G- and Klebsiella G-). Sterilized needles were used to transfer pathogens to the nutrient agars. Distilled water was used in the measurement as negative control. The plates were placed at room temperature for 1 h for diffusion and incubated at 37 °C for 24 h. The diameters of the clear zone of inhibition were measured by scale and recorded. Compounds showing promising antimicrobial activity were selected for minimum inhibitory concentration studies. The minimum inhibitory effect of the Salen metal complexes were determined by micro well dilution technique using Muller-Hinton broth as culture media by two fold serial dilutions. Two concentrations for each complex were prepared at (0.0125 and 0.0250 mg/ml).[15]

Results and Discussion

Chiral bimetallic complexes (1-5) have been prepared by treating a punch of metal chloride with proligand Salen. The Salen ligand system which host two divalent M(II) metal center. The complexes (1-5) were stable at room temperature and less soluble in organic solvents except in DMSO. Several attempts were failed to grow single crystals suitable X-ray crystal structure analysis due to solubility difficulties. A set of accurate spectroscopic analyses such as IR spectra, NMR spectrum, and mass spectrometry were used to characterize complexes.

\[[\text{CoCl}_2(\text{Salen})]\] (1)

Complex (1) was synthesized in an excellent yield (0.25 g, 96 %, m. p. 233-235 °C) by a simple one pot metathesis reaction between CoCl₂ and proligand (Salen) (equation 2). IR (KBr): \(\tilde{\nu} = 3026\) (s), 2500 (w), 1972 (w), 1603 (s), 1485 (s), 1438 (w), 1317 (m), 1169 (m), 1028 (s), 961 (s), 891 (m), 808 (s), 468 (s) Fig. (1). \(^1\text{H}-\text{NMR}\) (400 MHz, C₆D₆, 25°C): \(\delta = 10.26\) (s, 2H, OH), 8.35-7.26 (m, 8H, Ar), 6.67 (d, 2H, CH=N-), 4.15-2.50 (m, 4H, CH₂).

\[[\text{NiCl}_2(\text{Salen})]\] (2)
Similar product (2) in a very good yield (0.21 g, 84 %, m. p. 228-230 °C) obtained from the preliminary reaction as described for complex (1). IR (KBr): \( \tilde{\nu} = 3460 \text{ (s)}, 3332 \text{ (s)}, 2925 \text{ (w)}, 2397 \text{ (w)}, 2188 \text{ (w)}, 2097 \text{ (w)}, 1635 \text{ (s)}, 1603 \text{ (s)}, 1494 \text{ (m)}, 1455 \text{ (w)}, 1411 \text{ (s)}, 1283 \text{ (s)}, 1147 \text{ (w)}, 1109 \text{ (m)}, 1032 \text{ (w)}, 1015 \text{ (m)}, 975 \text{ (m)}, 853 \text{ (s)}, 705 \text{ (s)}, 561 \text{ (s)}, 418 \text{ (w)} \) Fig. (2). \(^1\text{H-NMR (400 MHz, C}_6\text{D}_6\text{, }25^\circ\text{C}): \delta = 10.22 \text{ (s, 2H, OH)}, 8.49-7.11 \text{ (m, 8H, Ar)}, 6.65 \text{ (d, 2H, CH=N-)}, 3.37-2.49 \text{ (m, 4H, CH}_2\text{).}

\[(\text{CuCl}_2)_{2}(\text{Salen})\] (3)

Similarly complex 3 prepared in an excellent yield (0.24 g, 92 %, m. p. 215-217 °C) by employing the same reaction conditions that described for complexes 1. IR (KBr): \( \tilde{\nu} = 3572 \text{ (s), 3123 \text{ (w), 3038 \text{ (s), 2950 \text{ (w), 2556 \text{ (w), 2490 \text{ (w), 2506 \text{ (w), 1962 \text{ (w), 1875 \text{ (w), 1633 \text{ (s), 1593 \text{ (m), 1542 \text{ (s), 1502 \text{ (m), 1443 \text{ (s), 1392 \text{ (s), 1333 \text{ (m), 1279 \text{ (s), 1201 \text{ (s), 1155 \text{ (w), 1125 \text{ (w), 1054 \text{ (s), 1009 \text{ (w), 898 \text{ (s), 759 \text{ (s), 654 \text{ (w), 599 \text{ (m), 524 \text{ (m), 483 \text{ (m)} \) Fig. (3). 1H-NMR (400 MHz, C}_6\text{D}_6\text{, }25^\circ\text{C): } \delta = 9.25 \text{ (s, 2H, OH)}, 8.14 \text{ (br, 8H, Ar)}, 3.42 \text{ (s, 2H, CH=N-)}, 3.03-2.50 \text{ (m, 4H, CH}_2\text{).}

\[(\text{SnCl}_2)_{2}(\text{Salen})\] (4)

Complex 4 was afforded in a very good yield (0.22 g, 84 %, m. p. 268-270 °C) by reaction SnCl\(_2\) with Salen proligand in a molar ratio 1:1. IR (KBr): \( \tilde{\nu} = 3478 \text{ (m), 2580 \text{ (w), 2390 \text{ (w), 2305 \text{ (w), 2054 \text{ (w), 1927 \text{ (w), 1686 \text{ (w), 1596 \text{ (s), 1489 \text{ (s), 1444 \text{ (w), 1329 \text{ (m), 1169 \text{ (m), 1030 \text{ (s), 966 \text{ (s), 801 \text{ (m), 814 \text{ (s), 779 \text{ (w), 607 \text{ (m), 476 \text{ (s)}} Fig. (3). 1H-NMR (400 MHz, C}_6\text{D}_6\text{, }25^\circ\text{C): } \delta = 12.69 \text{ (s, 2H, OH)}, 8.18-7.53 \text{ (m, 8H, Ar)}, 6.96 \text{ (s, 2H, CH=N-)}, 4.19-2.90 \text{ (m, 4H, CH}_2\text{).}

\[(\text{BaCl}_2)_{2}(\text{Salen})\] (5)

Following the same steps that described for complexes 1 lead to synthesise complex 5 in a very good yield (0.23 g, 88 %, m. p. 160-162 °C). IR (KBr): \( \tilde{\nu} = 3861 \text{ (m), 3460 \text{ (w), 2332 \text{ (w), 2925 \text{ (w), 2367 \text{ (w), 2188 \text{ (m), 2097 \text{ (m), 1635 \text{ (s), 1603 \text{ (m), 1494 \text{ (m), 1455 \text{ (m), 1411 \text{ (m), 1283 \text{ (s), 1207 \text{ (w), 1109 \text{ (w), 1032 \text{ (m), 1015 \text{ (m), 936 \text{ (w), 853 \text{ (s), 744 \text{ (w), 705 \text{ (w), 561 \text{ (s), 418 \text{ (w)} Fig. (3). 1H-NMR (400 MHz, C}_6\text{D}_6\text{, }25^\circ\text{C): } \delta = 13.30 \text{ (s, 2H, OH)}, 8.59-7.27 \text{ (m, 8H, Ar)}, 6.84 \text{ (s, 2H, CH=N-)}, 3.40 \text{ (m, 4H, CH}_2\text{).}

**FT-IR spectra**

FT-IR spectra (Figures 1-5) of Schiff base metal complexes showed a shift toward higher frequencies of azomethine \( \tilde{\nu} \text{ (C= N) group at 1635 cm}^{-1} \) due to the association of the metal ions with the azomethine group with a symmetric ring. These results are in agreement with previous reported complexes [16]. In addition to the nature of the metal ion and the associated atoms and the bonds that can shift the frequencies toward higher or lower field. Presence of medium intensity bands at 3535-2030 cm\(^{-1}\) in ligands may be assigned to \( \tilde{\nu} \) OH group.[17] The coordination of the ligand to the metal atoms through the azomethine nitrogen atom is further confirmed by the appearance of medium intensity bands in the range of 695-418 cm\(^{-1}\) due to \( \tilde{\nu} \) (M-N) vibrations.[18, 19] The spectra
also showed the disappearance of carbonate (C=O) belongs to aldehyde from staring material that confirming ligand synthesis successfully. Schiff bases were characterized by the appearance of bundles at the region (3155-3030) due to the (C-H) aromatic vibrations.

$^{1}$H-NMR spectra

$^{1}$H-NMR spectra of the compounds (1-5) were obtained and interpreted in DMSO at 25 °C. TMS was used as an internal standard. There is a clear change in characteristic signals of the free ligand after complexation that can help to understand the complexes behavior in solution. $^{1}$H-NMR spectra of all the complexes showed a kind of complexity or partially overlapped in the frequency of some protons confirming coordination of the metal ion. This due to the deshielding of protons as a result of the reduction of electron density after coordination. In addition, the dimerization that increased the complexity of the spectra, owing to the loss of symmetry consequent to the formation of the dinuclear species. In addition to the lack of a mirror plane in the equatorial ligand.[20] The $^{1}$H-NMR spectra of compounds (1-5) are given in Figs. 6-10 respectively. These figures showed the appearance of multiple beams in the aromatic region (7.11 - 8.59 ppm) related to the phenyl aromatic protons and the integrations of those protons found to be corresponded to the composition of each compound. While the spectra showed the appearance of two triplet bands in the region (2.49 - 4.19) to the methylene groups. The integration shows that the expected singlet of azomethine is appeared at around (6.00 ppm). The chemical shift observed for the (OH) protons in the ligand was observed in a high field. (OH) protons usually are hard to detect so some peaks appeared very small. Thus, the (OH) protons give rise between 13.30-9.25 ppm.

Mass spectra

The mass spectra of complexes 1, 2, 3, 4, and 5 were recorded at 70 V cone voltage to avoid the dissociation of the axial ligands. Because the relative intensity of the peaks depends on both the voltage and the nature of the substitution groups.

$\left[(\text{CoCl}_2)\text{2(Salen)}\right] \text{3H}_2\text{O}$ (1)

The molecular ion beam (M +.) of the complex $\left[(\text{CoCl}_2)\text{2(Salen)}\right] \text{3H}_2\text{O}$ was observed at 578.60 m/z on the Mass spectrum. The spectrum shows also two other peaks (calc. 563.88, found 564.60, calc; 527.86, found 523.50) (Fig. S3) corresponding to $\left[(\text{CoCl}_2)\text{2(Salen)}\right] \text{2H}_2\text{O}$ and $\left[(\text{CoCl}_2)\text{2(Salen)}\right]^+$ respectively. Consequently, complex $\left[(\text{CoCl}_2)\text{2(Salen)}\right]^+$ lost PhOH and Cl$_2$ (calc. 435.83, found 439.40; calc. 363.90, found 368.30). Then further fragments lost such as Cl and PhOH that showed the following peaks (calc. 328.93, found 325.10; calc. 271.87, found 271.30).

$\left[(\text{NiCl}_2)\text{2(Salen)}\right] \text{(2)}$
In the Mass spectrum of the complex \([\text{NiCl}_2\text{2(Salen)}].4\text{H}_2\text{O}\), the molecular ion beam (M +.) was appeared at m/z 591.60. The detection of the following peaks (calc. 581.89, found 577.60; calc. 563.60, found 563.88; calc. 543.87 found 551.60) are related to these fragments respectively \([\text{NiCl}_2\text{2(Salen)}].3\text{H}_2\text{O}\), \([\text{NiCl}_2\text{2(Salen)}].2\text{H}_2\text{O}\) and \([\text{NiCl}_2\text{2(Salen)}].\text{H}_2\text{O}\). Intense peak appeared at 523.60 contributed to \([\text{NiCl}_2\text{2(Salen)}]\) ion which in it is turn loses PhOH and Cl2 (calc. 433.84, found 437.40; calc. 398.87, found 393.40).

\([\text{CuCl}_2\text{2(Salen)}]\) (3)

The mass spectrum of \([\text{CuCl}_2\text{2(Salen)}]\) complex was investigated. The peak appears at 591.60 m/z is due to the molecular ion \([\text{CuCl}_2\text{2(Salen)}].3\text{H}_2\text{O}^+\). Three intense peaks (calc. 573.87, found 577.60; calc. 553.86, found 551.60; calc. 535.85, found 537.60) assigned to the following fragments \([\text{CuCl}_2\text{2(Salen)}].2\text{H}_2\text{O}\), \([\text{CuCl}_2\text{2(Salen)}].\text{H}_2\text{O}\) and \([\text{CuCl}_2\text{2(Salen)}]\). Last ion further lost fragments such as PhOH and Cl that showed two peaks at (calc. 443.83, found 451.40; calc. 408.86, found 409.40). These peaks confirm the proposed formula and coincides. The mass fragmentation pattern of the Cu(II) complex is depicted in (Figure 13).

\([\text{SnCl}_2\text{2(Salen)}]\) (4)

The mass spectra of \([\text{SnCl}_2\text{2(Salen)}]\) complex shows molecular ion peak at m/z 599.50. Complex showed another peak at (calc. 575.86 found 577.60) indicating the loss of Cl2. Intense peak appeared at (calc. 483.84 found 485.00) confirming PhOH fragment losing. Some fragments were found in which one or two units were less or more than the calculated value. Due to the isotopic abundance that resulting in a different overall mass.

\([\text{BaCl}_2\text{2(Salen)}]\) (5)

The mass spectrum of the complex \([\text{BaCl}_2\text{2(Salen)}]\), the molecular ion beam (M +.) was observed at m/z 592.70. The molecular ion of \([\text{BaCl}_2\text{2(Salen)}]\) complex loses PhOH and Cl leaving an ion at m/z (calc. 556.81, found 551.60), which by its turn, loses Cl2 giving an ion at m/z (calc. 486.87, found 481.50). Finally, the peak arising from the loss of PhOH fragment is presented in the mass spectra at (calc. 394.85, found 395.40) Fig. 15.

**Biological activity**

The prepared metal complexes (1-5) were screened in vitro for their anti-bacterial activity by the disc diffusion and microdilution methods according to the European Committee on Antimicrobial Susceptibility Testing and Clinical and Laboratory Standards Institute guidelines [15]. Biological activity of these compounds were tested against two different strains of human pathogenic gram negative bacteria (\(E\) coli \(G^-\) and \(Klebsiella\) \(G^-\)). The minimum inhibition concentrations (MICs) of
the compounds were also determined by employing two concentrations (0.0125 and 0.0250 mg/ml) (Table 1).

Approximately, all compounds at low concentration displayed good to moderate destruction activity against bacteria strains. Table 1 shows inhibition zone of Gram bacteria by the Schiff base metal complexes. It is observed that metal complex [(CoCl2)2(Salen)] at (0.0125 mg/ml) has significantly more antimicrobial activities against Klebsialla G- with inhibition zone (12 mm) than E coli G- with only (4 mm) inhibition zone. This clearly revealed that metal complex have profound impact on antibacterial activities. While both E coli and G- Klebsialla G- showed strong resistance toward [(NiCl2)2(Salen)] complex and even after concentration increased to (0.0250 mg/ml) the inhibition zone stay at (0 mm). This resistance bacteria showed because of these bacteria exposure to nickel complexes before that help it to build such strong resistance.[15] Complex [(CuCl2)2(Salen)] at (0.0125 mg/ml) concentration was showing promising antimicrobial activity against E coli and G- Klebsialla G- and inhibition zones were (10 mm and 4 mm) respectively. This antibacterial activity has increased significantly to (15 mm and 9 mm) when the complex dose has been doubled to (0.0250 mg/ml). While, complex [(SnCl2)2(Salen)] was found to be less active at (0.0125 mg/ml) against E coli G- and Klebsialla G- with inhibition zones (0 mm and 2 mm) respectively. Also both bacteria strains exhibited high level of resistance even after increasing concentration to (0.0250 mg/ml) bacteria continue growing. As seen in Fig. 17 and Table 1, inhibition activity of [(SnCl2)2(Salen)] against E coli G- was very limited even after increasing concentration to (0.0250 mg/ml) the inhibition zone was recorded only (2 mm).[21] But complex [(SnCl2)2(Salen)] works effectively against Klebsialla G- at (0.0125 mg/ml) and destruction effect has increased from 9 mm to 13 mm after the complex concentration doubled. The results are summarized in table 1, figure 17 and 18.[22, 23]

Conclusions

Highly air and moisture stable Salen metal complexes [(MCl2)2(Salen)] {M = Co (1), Ni (2), Cu (3), Sn (4), Ba (5)} synthesised simply in one step reaction pot by the direct reaction between the tetradentate ligand system (Eqn. 2) and different chloride metals. The complexes were characterized chemically with a variety of techniques such as ¹H-NMR, Mass spectrometry and IR spectroscopy. Studies of antibacterial properties with the broth microdilution technique by employing two different bacterial strains (E coli G- and Klebsialla G-) revealed a moderate to good activity of the prepared complexes.
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Figure 1: FT-IR spectrum of \([\text{CoCl}_2(\text{Salen})]\) complex.
Figure (2): FT-IR spectrum of [(NiCl₂)(Salen)] complex.
Figure (3): FT-IR spectrum of \((\text{CuCl}_2\text{)(Salen)})\) complex.
Figure (4): FT-IR spectrum of \([\text{SnCl}_2(\text{Salen})]\) complex.
Figure (5): FT-IR spectrum of \([\text{BaCl}_2\text{(Salen)}]\) complex.
Figure (6): $^1$H-MNR spectrum of [(CoCl$_2$)(Salen)] complex.
Figure (7): $^1$H-MNR spectrum of $[\text{NiCl}_2\text(Salen)]$ complex.
Figure (8): $^1$H-NMR spectrum of [(CuCl$_2$)$_2$(Salen)] complex.
Figure (9): $^1$H-MNR spectrum of $[\text{SnCl}_2(\text{Salen})]$ complex.
Figure (10): $^1$H-MNR spectrum of [(BaCl$_2$)$_2$(Salen)] complex.
Figure (11): Mass spectrum of [(CoCl$_2$)(Salen)] complex.
Figure (12): Mass spectrum of [(NiCl₂)(Salen)] complex.
Figure 13: Mass spectrum of \([\text{CuCl}_2\text{Salen}]\) complex.
Figure (14): Mass spectrum of \([\text{SnCl}_2(\text{Salen})]\) complex.
Figure (15): Mass spectrum of \((\text{BaCl}_2)(\text{Salen})\) complex.
Table 1: The effects of chemical compounds (inhibition zone) on Gr-bacteria (*E coli* and *Klebsiella*).

| Types of isolates | Chemical compounds concentrations |
|-------------------|-----------------------------------|
|                   | [(CoCl₂)L] | [(NiCl₂)L] | [(CuCl₂)L] | [(SnCl₂)L] | [(BaCl₂)L] | [(NiCl₂)L] | [(CuCl₂)L] | [(SnCl₂)L] | [(BaCl₂)L] |
| Concentration g/mL| *3 (0.0125)| *5 (0.0125)| *2 (0.0125)| *1 (0.0125)| *4 (0.0125)| *6 (0.0250)| *8 (0.0250)| *9 (0.0250)| *7 (0.0250)|
| *E coli*          | 4 mm       | 0 mm       | 10 mm      | 0 mm       | 0 mm       | 15 mm      | 0 mm       | 0 mm       | 2 mm       |
| *Klebsiella*      | 12 mm      | 0 mm       | 4 mm       | 2 mm       | 9 mm       | 0 mm       | 9 mm       | 0 mm       | 13 mm      |

L = Salen, *number = number described on bacterial disc
Figure 16: Showing inhibition zones of Klebsiella G- by the effect of (1-5).

Figure 17: Showing inhibition zones of E coli G- by the effect of (1-5).