Mono and binuclear cobalt(II) mixed ligand complexes containing 1,10-phenanthroline and adenine using 1,3-diaminopropane as a spacer: synthesis, characterization, and antibacterial activity investigations

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Abstract

Background: Coordination compounds, in particular cobalt(II) mixed ligand complexes containing 1,10-phenanthroline, have drawn the attention of many investigators as some of them are showing antimicrobial activities.

Result: Herein, we report three novel mixed ligand complexes of cobalt(II) having the formulae [Co(L₁)₂(H₂O)₂]Cl₂, [Co(L₁)₂(L₃)(H₂O)]Cl₂ and [Co₂(L₁)₄(L₃)₂(L₄)]Cl₄ (L₁ = 1,10-phenanthroline, L₂ = adenine, L₃ = 1,3-diaminopropane) were synthesized and characterized by elemental analysis, conductivity measurement, infrared, and UV-Vis spectroscopic techniques. Octahedral geometries are proposed to all the complexes. In vitro antibacterial activities of the ligands, salt, and metal complexes were tested on four pathogenic bacteria (Staphylococcus aureus, Salmonella typhus, Escherichia coli, and Staphylococcus epidermis) using disc diffusion method.

Conclusions: It is interesting to note that the newly synthesized cobalt(II) complexes are active against gram negative bacteria (Escherichia coli and Klebsiella pneumoniae) even though cobalt(II) complexes are well known for their activity against gram positive bacteria.

Keywords: Binuclear, Cobalt(II) complex, 1,10-Phenanthroline, Adenine, 1,3-Diaminopropane, Antibacterial activity

Background

On coordination with suitable ligands, it is possible to impose a set of desired properties on transition metals for specific applications. It is achieved by altering properties such as the stability of different oxidation states, solvophilicity, electrophilic, and nucleophilic properties of the metal ions. It can be done by tuning through variation of the metal and the choice of one of the vast array of ligands available for complexation [1–3]. While coordinating, the properties of the ligands themselves are also modified. For instance, the pharmacological activities and their crucial role in DNA/RNA base pairing through several hydrogen-bonding patterns of free purines such as adenine can significantly change after complex formation [4–6]. 1,10-Phenanthroline significantly changes its toxicity when coordinated to metals [7, 8]. Based on this, synthesis of different coordination compounds with one or more metal centers by ligand tailoring has become a fascinating research field. Designing such coordination compounds for therapeutic applications has been part of this activity [9–18].

A good number of mononuclear [4, 7, 19, 20] and binuclear [21–25] mixed ligand metal complexes have...
been reported. In particular, the bioinorganic chemistry of cobalt(II) complexes have drawn the attention of many investigators [26–28]. This is because of the fact that cobalt complexes are showing antibacterial [29] and antifungal [30] activities. However, in most reports, Co(II) complexes are unable to show activities against Gram-negative bacteria [31]. This is probably due to their inability to penetrate the cell wall of these bacteria [32–34], which demands the fine-tuning of Co(II) complexes employing novel ligand functionalities, thereby achieving variable compositions. In this context, two mononuclear and one binuclear Co(II) complexes have been synthesized from 1,10-phenanthroline, adenine, and 1,3-diaminopropane, and their biological activities were studied and are compared with commercially available antibiotics.

1,10-Phenanthroline (Fig. 1) is rigid planar, chelating bidentate ligand. The stacking interaction of 1,10-phenanthroline with DNA base pairs makes it applicable in medical fields [35, 36].

Adenine (Fig. 2) is a purine nucleotide and can exist in either amino or imino forms. However, the amino tautomer is more stable and therefore predominates under the cellular conditions [37]. Its exocyclic amino group is less likely to coordinate since the lone pair of electrons is largely delocalized into the ring by resonance (Fig. 3). Because it is free from resonance and steric hindrance, the best coordination site for adenine is N7 of the imidazole ring [38].

Metal complexes of adenine have considerable interest in the design of model complexes involving purines which could mimic interactions of metal ions with DNA [39]. 1,3-Diaminopropane is a bidentate ligand (Fig. 4) which is used as a precursor for pharmaceutical, agrochemical, and organic industries [40, 41].

**Methods**

**Materials**
The metal salt is CoCl2.6H2O (Analar BDH) and the ligands are 1,10-phenanthroline monohydrate (BDH), adenine (99%, ACROS), and 1,3-diaminopropane (ACROS). Muller Hinton Agar and barium chloride (BLULUX Laboratories Ltd, India) were used as such. All other solvents used are of reagent quality.

**Physical methods of analysis**
All the complexes were analyzed for their metal and halide contents by the conventional methods. The molar conductance was measured using 10^{-3} M solution for
each complex in deionized water with JENWAY 4200 conductivity meter at room temperature. The electronic spectra were recorded in the 50,000–12,500 cm$^{-1}$ region on Sanyo SP65 UV/VIS spectrophotometer. IR spectra were recorded using KBr discs in the 4000–400 cm$^{-1}$ region on AVATAR 330 FT-IR, Thermo Nicolet spectrophotometer. C, H, and N content determination were performed on a Perkin Elmer 2400 elemental analyzer.

Synthesis of complexes

**Synthesis of** $[\text{Co}(\text{L}_1)_2(\text{H}_2\text{O})_2]\text{Cl}_2$ (1)

A methanolic solution of 1,10-phenanthroline monohydrate (1 g, 5 mmol) was added to a methanolic solution of CoCl$_2$.6H$_2$O (0.6 g, 2.5 mmol) being stirred magnetically in an ice bath. It was further allowed to stir for 1 h at room temperature. It was then refluxed for one more hour and allowed to cool to room temperature. On evaporating the resultant solution, a yellow powder, which was obtained and washed with acetone several times to remove any unreacted 1,10-phenanthroline. It was then re-crystalized from methanol (yield, 1.14 g; 85.84%).

**Synthesis of** $[\text{Co}(\text{L}_1)_2(\text{L}_2)(\text{H}_2\text{O})]\text{Cl}_2$ (2)

To an aqueous solution of 1 (0.3 g, 0.57 mmol) being stirred magnetically in oil bath at 60 °C, an aqueous solution of adenine (0.077 g, 0.57 mmol) was added. A deep reddish brown homogeneous solution was obtained. The solvent was removed under vacuum. Yellowish orange powder was collected and washed several times with acetonitrile (yield, 0.23 g; 62.9%).

**Synthesis of** $[\text{Co}_2(\text{L}_1)_4(\text{L}_2)_2(\text{L}_3)]\text{Cl}_4$ (3)

To an aqueous solution of 2 (0.320 g, 0.49 mmol) being stirred magnetically in water bath at 10 °C, an aqueous solution of slightly excess 1,3-diaminopropane (0.022 g, 25 μL) was added. A deep reddish brown homogeneous solution was obtained. The stirring was continued for one more hour. The solvent was removed from the resulting solution under vacuum. A red-brown powder was obtained and was washed with acetone several times (yield, 0.266 g; 73%).

**Results**

**Synthesis and characterization studies**

The formation of the complexes can be represented by the following equations (scheme 1):

$\text{CoCl}_2$.6H$_2$O + 2L$_1$ $\rightarrow$ $[\text{Co}(\text{L}_1)_2(\text{H}_2\text{O})_2]\text{Cl}_2$ (1)

$[\text{Co}(\text{L}_1)_2(\text{H}_2\text{O})_2]\text{Cl}_2 + \text{L}_2$ $\rightarrow$ $[\text{Co}(\text{L}_1)_2\text{L}_2\text{H}_2\text{O}]\text{Cl}_2$ (2)

$[\text{Co}(\text{L}_1)_2\text{L}_2\text{H}_2\text{O}]\text{Cl}_2 + \text{L}_3$ $\rightarrow$ $[\text{Co}_2(\text{L}_1)_4(\text{L}_2)_2(\text{L}_3)]\text{Cl}_4$ (3)

where L$_1$ = 1,10-phenanthroline, L$_2$ = Adenine, and L$_3$ = 1,3-diaminopropane.
plexes and the commercial antibiotic demonstrated that the complexes are presented in Table 3. It has been observed that complex 3 is having better biological activity than the corresponding precursor complexes 1 and 2 against all the bacterial strains in the present study (Table 4).

The activity indexes of the present study with respect to the commercial antibiotic demonstrated that the complex is a strong confirmation of the rigid and symmetric configuration of the rest of the complex. The strong and broad band ranging from 3403 to 3043 cm$^{-1}$ is due to the additive combination of the characteristic vibrations of primary amine from adenine and 1,3-diaminopropane which is a strong confirmation of the coordination of 1,3-diaminopropane to [Co(L1)2(H2O)]Cl2. Moreover, the increase in strength and broadness of the band in the frequency range 3403–3043 cm$^{-1}$ as well as the appearance of new bands at the vibration frequency 539 cm$^{-1}$ is due to Co–N bond confirms the coordination of 1,3-diaminopropane in the formation of the binuclear complex.

**Electronic spectra**

Inter-ligand and simple characteristic d-d transitions are exhibited by the complexes. Significant difference in the

| Complexes | Molar mass (g / mol) | Melting point/°C | Color/ appearance | Yield (%) | Elemental analysis, calculated (found) (%) | $\lambda_m$ (molar conductivity), S cm$^2$ mol$^{-1}$ |
|-----------|---------------------|-----------------|-------------------|-----------|----------------------------------------|-----------------------------------------------|
| [Co(L1)2(H2O)]Cl2 | 526.29 | 360 | Yellow powder | 85.84 | Co 11.22, Cl 13.50, C 54.77, H 3.83, N 10.65 | 138.6 |
| [Co(L2)2(L3)Cl2] | 643.90 | 256 | Yellow-orange powder | 62.90 | Co 9.16, Cl 11.01, C 54.01, H 3.60, N 19.58 | 129.4 |
| [Co2(L1)2(L2)2(L3)]Cl2 | 1324.83 | 245 | Brownish-red powder | 73.00 | Co 8.90, Cl 10.70, C 55.30, H 3.95, N 21.15 | 154.2 |

**Table 2** Characteristic IR absorption (cm$^{-1}$) of ligands L1, L2, and L3 and complexes 1, 2, and 3

| Compound | $\nu$(C−C) | $\nu$(C−N) | $\nu$(C−H) | $\nu$(N−H) | $\nu$(C−OH) | $\nu$(C−N) |
|----------|------------|------------|------------|------------|------------|------------|
| L1       | 1581       | 1610       | 3043       | -          | 3422       | -          |
| L2       | 1582       | 1605       | 2689       | 3290       | -          | 1230       |
| L3       | -          | -          | 2800       | 3350, 2950 | -          | 1100       |
| [Co(L1)(H2O)]Cl2 | 1587 | 1626 | 3048 | - | 3425 | - |
| [Co(L2)(H2O)]Cl2 | 1607 | 1664 | 3118 | Overlapped with OH | 3442–3139 | 1383 |
| [Co2(L1)2(L2)2(L3)]Cl2 | 1587 | 1632 | 3189 | 3450–3062 | - | 1387 |
band number and position of transition absorption between CoCl₂.6H₂O, the ligands, and the complexes is observed. This may be as a consequence of different environments around the metal ion following the coordination [42–44]. The coordination of the ligands to the metal is demonstrated by the shifts in the maximum absorption wave lengths corresponding to ligand centered π → π*(C=C), π → π*(C=N), n → π*(C=N) as well as metal centered energy states. The absorption band at 37,878 cm⁻¹ of 1,10-phenanthroline due to n → π*(C=N) is shifted to 37,313; 37,174; and 36,764 cm⁻¹ in the complexes 1, 2, and 3, respectively [45]. Furthermore, the single band due to the simple d-d transition in the starting salt CoCl₂.6H₂O observed at 23,419 cm⁻¹ is changed to triple absorption bands between 44,062 and 13,642 cm⁻¹ in the complexes 1, 2, and 3, respectively. Therefore, the single band due to the simple d-d transition in the starting salt CoCl₂.6H₂O observed at 23,419 cm⁻¹ is changed to triple absorption bands between 44,062 and 13,642 cm⁻¹ in the complexes 1, 2, and 3, respectively.

The percentage activity indexes against the reference antibiotics showed better biological activities than the precursor complexes 1 and 2 against all the tested strains (Table 4). Based on the proposed structure, it is expected that complex 3 is having configurationally free twisting movement through the bridge, which presumably enhanced its flexibility and in turn enhances the penetration power of the complex into the cytoplasm of the pathogenic cells [47].

**Table 3** Electronic spectral data of the salt and complexes

| Compounds | Absorption bands (cm⁻¹) | Tentative assignments |
|-----------|-------------------------|----------------------|
| L₁        | 43,103; 37,878          | n; n → n*            |
| L₂        | 34,602                  | n → n*               |
| L₃        |                        |                      |
| [Co(L₁₂)₂(H₂O)]Cl₂  | 44,052; 37,313; 22,624; 15,748; 13,440 | n → n*, π → π*; 4T₁g(F) → 4T₁g(P); 4T₁g(F) → 4A₂g(F) π → 4T₂g(F) |
| [Co(L₁₂)₂(H₂O)]Cl₂  | 43,103; 37,174; 22,371; 15,948; 13,280 | n → n*, π → π*; 4T₁g(F) → 4T₁g(P); 4T₁g(F) → 4A₂g(F) π → 4T₂g(F) |
| [Co(L₁₂)₃(L₃₂)]Cl₄  | 44,052; 36,764; 21,929; 18,518; 13,642 | n → n*, π → π*; 4T₁g(F) → 4T₁g(P); 4T₁g(F) → 4A₂g(F) π → 4T₂g(F) |

**Antibacterial activity**

Antibacterial activity is occurring because of the diffusion of the complexes through the lipid membrane of the cells and interacting with the normal activity of the cell. This can be varied by designing the complexes with varying lipophilic properties. The interaction of the complexes with targeted cell could be achieved by tuning the complex in such a way that its components have properties either that bind covalently (irreversible) or interact non-covalently, but deliver active ligands in vivo to the biological target [46]. It has been observed that complex 3 showed better biological activities than the precursor complexes 1 and 2 against all the tested strains (Table 4). Based on the proposed structure, it is expected that complex 3 is having configurationally free twisting movement through the bridge, which presumably enhanced its flexibility and in turn enhances the penetration power of the complex into the cytoplasm of the pathogenic cells [47].

**Minimum inhibitory concentration (MIC) determination**

Minimum inhibitory concentration (MIC) is the lowest concentration that completely inhibited the growth of microorganisms for 24 h. Around 100 μg/mL of complex 3 is sufficient to inhibit the growth of all the tested strains (Fig. 6). The percentage activity indexes against the reference antibiotic demonstrated that the complexes are less

**Table 4** Antibacterial activity of CoCl₂.6H₂O, ligands, metal complexes, and reference antibiotic

| Compound       | Escherichia coli (± SD) | Salmonella typhus (± SD) | Staphylococcus aurous (± SD) | Staphylococcus epidermis (± SD) |
|----------------|-------------------------|--------------------------|------------------------------|--------------------------------|
| CoCl₂.6H₂O     | 10.50 ± 0.00            | 11.33 ± 0.58             | 12.08 ± 1.01                 | 13.92 ± 0.14                   |
| L₁             | 27.33 ± 0.57            | 35.33 ± 0.28             | 34.83 ± 0.29                 | 27.28 ± 0.29                   |
| L₂             | 0.00 ± 0.00             | 0.00 ± 0.00              | 0.00 ± 0.00                  | 0.00 ± 0.00                    |
| L₃             | 40.00 ± 0.00            | 50.17 ± 0.29             | 54.50 ± 0.50                 | 43.92 ± 0.14                   |
| [Co(L₁₂)₂(H₂O)]Cl₂ | 23.76 ± 0.57           | 23.92 ± 0.14             | 23.25 ± 0.66                 | 22.50 ± 1.32                   |
| [Co(L₁₂)₂(H₂O)]Cl₂ | 21.33 ± 0.57           | 20.50 ± 0.00             | 19.53 ± 0.50                 | 20.17 ± 0.29                   |
| [Co(L₁₂)₃(L₃₂)]Cl₄ | 20.67 ± 0.57           | 19.50 ± 0.50             | 18.67 ± 0.58                 | 19.25 ± 0.43                   |
| Methanol       | 42.75 ± 0.25            | 42.67 ± 0.58             | 44.83 ± 0.29                 | 40.83 ± 0.29                   |
| Water          | 0.00 ± 0.00             | 0.00 ± 0.00              | 0.00 ± 0.00                  | 0.00 ± 0.00                    |
| Ciprofloxacin  | 35.25 ± 0.25            | 40.50 ± 0.50             | 29.92 ± 0.38                 | 36.08 ± 1.01                   |
active. However, it is evident that the MIC of the binuclear complex 3 is far better than complexes 1 and 2 (Table 5). This is probably because of bisintercalation due to the two planar intercalating 1,10-phenanthroline ring systems covalently linked 1,3-diaminepropane.

**Table 5** The percentage activity index data of the complexes against the tested bacteria compared ciprofloxacin

| Compound | Microorganism          | Escherichia coli | Salmonella typhus | Staphylococcus aureus | Staphylococcus epidermis |
|----------|------------------------|------------------|-------------------|----------------------|-------------------------|
| [Co₂(L₁)₄(L₂)₂L₃]Cl₄ | – 0.32                | – 0.40           | – 0.22            | – 0.38               |
| [Co(L₁)₂(L₂)(H₂O)]Cl₂ | – 0.39                | – 0.49           | – 0.35            | – 0.44               |
| [Co(L₁)₂(H₂O)₂]Cl₂   | – 0.41                | – 0.59           | – 0.38            | – 0.47               |

**Discussion**

All the synthesized complexes are soluble in most polar solvents like acetonitrile, DMSO, and water and insoluble in almost all non-polar solvents. From the elemental analysis and conductivity measurement data, it can
be concluded that the complexes can be formulated as 
\[ \text{Co}(L_1)_2(H_2O)Cl_2 \] (1), \[ \text{Co}(L_1)_2(L_2)(H_2O)Cl_2 \] (2), and \[ \text{Co}_2(L_1)_4(L_2)_2L_3Cl_4 \] (3). The molar conductance data of the complexes 1, 2, and 3 was measured using 10^{-3} M solution for each complex in water and indicates a 1:2 conducting nature for 1 and 2 while a 1:4 conducting nature for 3. So, the complexes can be formulated as \[ \text{[Co}(L_1)_2(H_2O)]Cl_2 \] (1), \[ \text{[Co}(L_1)_2(L_2)H_2O]Cl_2 \] (2), and \[ \text{[Co}_2(L_1)_4(L_2)_2L_3]Cl_4 \] [48, 49]. The results obtained from infrared and electronic spectra are in conformity with the above derived formulae.

Based on the analytical and spectroscopic results presented, a distorted octahedral geometry is assigned for all the complexes. The antibacterial activity studies revealed that all the synthesized complexes exhibited antibacterial activity against even the most drug resistant Klebsiella pneumoniae which makes them as potential wide range antibacterial drugs, after in vivo cytotoxicity investigations. The major limitations of these synthesized complexes are that they show minimum inhibition zone than the reference antibiotic ciprofloxacin. However, their antibacterial activity can be improved by tuning the ligand functionality.

**Conclusion**

Novel mixed ligand Co(II) complexes have been prepared and characterized by various physical, chemical, and spectroscopic techniques. An octahedral geometry has been suggested for all synthesized complexes. Presumably, adenine is coordinated to Co(II) through its
ring nitrogen (N₂). Consequently, the complexes are expected to interact at least by hydrogen bonding with thymine residue of the bacteria genetic material. Furthermore, the synthesis resulted in the alteration of the properties of the starting materials. One advantage of this alteration is to enable the complexes to penetrate the cell wall of the pathogenic cells and consequently, interfere in their normal system to inhibit their growth. This was confirmed from the in vitro antibacterial test results. The result revealed that all the synthesized complexes exhibited antibacterial activity against even the most drug resistant *Klebsiella pneumoniae* which makes them, potentially wide range antibacterial drugs, after in vivo cytotoxicity investigations.

Even though the ligands and the synthesized complexes show antibacterial activity, they are not recommended as antibiotics as compared to the reference ciprofloxacin as the antibacterial activity is less for the complexes than the control. So, more work is needed to be done with respect to the variation of the ligands by causing conformational change to the complexes to achieve a good antibiotic drug by the complexes for therapeutic applications.

Acknowledgements
The authors are grateful to Bahir Dar University and Addis Ababa Science and Technology University for providing all necessary facilities.

Authors’ contributions
The authors YB, MB, and TG participated in conceptualizing, executing, analyzing, and writing the original draft except the authors AA, MT, and WL who were responsible for supervision, editing, and reviewing of this article. Also all authors have read and approved the manuscript.

Funding
Not applicable.

Availability of data and materials
Data are available from the corresponding author upon request.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing of interest.

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Received: 3 September 2019 Accepted: 16 April 2020
Published online: 19 May 2020

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